

Investigating the Effect of Micronutrients on Chronic Insomnia in Teachers:

A Multiple-Baseline Design

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by

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## Abstract

Over the last six years, Canterbury residents have lived through two major earthquakes and thousands of aftershocks, with such events negatively impacting psychological health. Research shows rates of post-traumatic stress symptoms in children have doubled post-quake, and a classroom containing children who are experiencing chronically high physiological arousal has been shown to be a stressful environment for teachers. Such stress therefore negatively impacts teachers' ability to sleep well, meaning many Christchurch teachers may suffer from insomnia, a debilitating condition leading to psychological distress and often comorbid with other mental health conditions. The present research sought to investigate the use of a broad-spectrum micronutrient formula called EMPowerplus (EMP+) for chronic insomnia in teachers. This study examined the effect of EMP+ over an 8-10 week period using a multiple-baseline design with placebo. Seventeen teachers were randomized to one of three baseline sequences where they completed a one week baseline period, before receiving five, nine, or 14 days, of placebo as well as 8-10 weeks of the micronutrient formula. After completion of the trial, a three-month follow up was conducted. All participants completed the trial, and results showed a statistically reliable and clinically significant decrease in insomnia severity (Cohen's  $d_{av} = -1.37$ ), on at least one or more aspects of the sleep diary, and on emotional exhaustion (Cohen's  $d_{av} = -1.08$ ). EMP+ also statistically significantly reduced insomnia severity compared to placebo (Cohen's  $d_{av} = -0.66$ ). Statistically significant reduction was not seen in stress, anxiety and depression scores as compared to placebo, and these levels were not generally clinically raised to begin with. Sixteen out of 17 participants were compliant, and side effects were generally mild and transitory. The current study provides evidence for the beneficial effect of micronutrient supplementation on chronic insomnia in Christchurch teachers working in a stressful environment. Future research incorporating measurement of nutritional intake and pro-inflammatory biomarkers, as well as conducting comparisons to other conventional treatments, is recommended.

## **List of Abbreviations**

ADHD: Attention-Deficit/Hyperactivity Disorder  
ATP: Adenosine triphosphate  
BDI: Beck Depression Inventory  
BZD's: Benzodiazepine  
CBT-I: Cognitive behavioural therapy for insomnia  
CRP: C-reactive protein  
CSD-M: Consensus Sleep Diary-Morning  
DASS: Depression, Anxiety and Stress Scale  
DSD: Daily Self Defense  
EEG: Electroencephalographic  
EMP+: EMPowerplus  
ETC: Electron transport chain  
GABA: Gamma-aminobutyric acid  
GI: Gastrointestinal  
GSH-Px: Glutathione peroxidase  
Ig: Immunoglobulin (e.g., IgA, immunoglobulin A)  
IL: Interleukin (e.g., IL-1, IL-6)  
LPS: Lypopolysaccharide  
MBI-ES: Maslach Burnout Inventory-Educators Survey  
MDA: Malondialdehyde  
MDA: Malondialdehyde  
NMDA: N-methyl-D-aspartate  
Non-BZD's: non-benzodiazepine  
NREM: Non Rapid Eye Movement  
OCD: Obsessive compulsive disorder  
OS: Oxidative stress  
PIRS-20: Pittsburgh Insomnia Rating Scale-20  
PSQI: Pittsburgh Sleep Quality Index  
PTS: Post-Traumatic Stress  
PTSD: Post-Traumatic Stress Disorder  
RCT: Randomized controlled trial  
REM: Rapid Eye Movement  
ROS: Reactive oxygen species  
SE%: Sleep efficiency percentage  
SOD: Superoxide dismutase  
SOL: Sleep onset latency  
SWS: Slow Wave Sleep  
TBARS: Thiobarbituric acid reactive substances  
TNF-a: Tumor necrosis factor alpha  
TST: Total sleep time

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## **1. Introduction**

On September 4<sup>th</sup> 2010, at 4:35am local time, the region of Canterbury, New Zealand and its main city, Christchurch (population approximately 400,000), was struck by a 7.1 magnitude earthquake (Gledhill, Ristau, Reyners, Fry, & Holden, 2011). Despite widespread infrastructure and property damage throughout the region, miraculously there were no fatalities and few injuries. Five months later on February 22<sup>nd</sup> 2011, at 12:51pm local time, a second earthquake (an aftershock of the initial event) struck the region. This 6.3 magnitude earthquake resulted in 185 fatalities and injured thousands both physically and psychologically. As well as this great loss Christchurch once again faced extensive and economically debilitating infrastructure damage, including building collapses throughout the city (Newell, Johnston, & Beaven, 2012). In the subsequent years the region has now experienced over 22,400 aftershocks ([www.quake.crowe.co.nz](http://www.quake.crowe.co.nz)). Both the immediate and persistent effects of these Christchurch earthquakes have exposed thousands of individuals to numerous psychological stressors over the years.

### **1.1 Psychological outcomes of natural disasters**

Earthquakes are natural disasters that are aversive, uncontrollable and unpredictable, thereby impacting psychological health and general wellbeing. Many studies have recorded the psychological impact that natural disasters can have on individuals, including fear, increased anxiety, post-traumatic stress (PTS), and depression (Bonanno, Brewin, Kaniasty, & Greca, 2010; Fergusson, Horwood, Boden, & Mulder, 2014; V. A. Johnson & Ronan, 2014; Nolen-Hoeksema & Morrow, 1991; Norris, Murphy, Baker, & Perilla, 2004; Rucklidge et al., 2012; Rucklidge, Blampied, Gorman, Gordon, & Sole, 2014). Moreover, higher rates of psychological distress in both adults and children following major earthquakes are evident around the world (Bödvarsdóttir & Elklit, 2004; Şalcıoğlu & Başoğlu, 2008; Yabe et al., 2014). Recent research found that after the Christchurch September earthquake, individuals were experiencing higher rates of stress, anxiety, and depression, as well as sleeplessness and cognitive dysfunction

(Dorahy & Kannis-Dymand, 2012; Kemp, Helton, Richardson, Blampied, & Grimshaw, 2011). Moreover, some studies posited that for individuals remaining in Christchurch after the February earthquake, feelings of tiredness, chronic stress, and uncertainty became the new norm (Gawith, 2013; Rowney, Farvid, & Sibley, 2014).

These heightened stress levels have been maintained by many individuals six years on (Norris, 2016). This is likely a result of ongoing-secondary stressors (i.e., situations that have persisted longer than the event of the earthquakes) (Bellamy, 2014; Lock et al., 2012) such as aftershocks (Radio New Zealand, 2016c), damage and loss resulting in loss of accommodation, employment, social support, and education networks, with property damage leading to thousands of insurance claims, many associated with difficult negotiations, as well as temporary or permanent residential relocation (CERA, 2014; Goodyear, 2014; Howden-Chapman et al., 2014; Wood, Noy, & Parker, 2016). Job loss and instability also resulted in which thus places financial pressure and strain on families (Garner, 2011; Gawith, 2013; Hartevelt & Small, 2011; Lock et al., 2012). These pressures are likely to disrupt normal daily family functioning and routine, therefore increasing the risk of deterioration in familial relationships (Lock et al., 2012). This has held true for Christchurch residents (Carville, 2013; Styliano & Carville, 2012; Towle, 2014). Additionally, high stress levels have further been maintained over the years as a result of continuing road works, worsened traffic, loss of community facilities, and decreased social connectedness (e.g., through relocating to another community or neighbours relocating or moving away from the city) (CERA, 2014).

These persistent on-going stressors have had a large impact on many Christchurch residents' wellbeing and psychological health, with research showing a 39% increase in adult mental health service use since mid-2012 (Carville, 2016; CERA, 2014; Humphrey & Renison, 2015; McCrone, 2015; Stewart, 2015). This is consistent with previous research showing the persistence of mental health disorders many years after the initial event of a disaster (Hussain, Weisaeth, & Heir, 2011; van der Velden, Wong, Boshuizen, & Grievink, 2013). This evidence

shows that Christchurch residents have lived in a stressful environment over the last six years; and although many residents may have recovered from their experiences, there is still a long road ahead for some.

### **1.1.1 Impact of earthquakes on schools**

The February 2011 earthquake had a tremendous impact on both primary (i.e., elementary school, New Entrants to year eight, with children aged from five years old to typically 13 years) and secondary schools (Years 9 to 13, with adolescents aged typically from 14 to 18) throughout the region. As a result, in order to resume schooling, some affected schools were co-located with schools residing in less damaged areas until decisions regarding repairs and rebuilding were made. The duration of these arrangements ranged from several weeks to years (Ham, Cathro, Winter, & Winter, 2012), with some continuing beyond 2017 (E. Murphy & Moir, 2016). Final decisions regarding the affected schools' futures were made in November 2013, when it was announced that 11 schools were to be merged to establish five merged schools, 11 additional schools closed and two additional schools closed voluntarily due to roll decline since the earthquake (APNZ, 2014; CERA, 2014; Davis, 2016; Young, 2016). These decisions resulted in relocation of children to new or different schools and job losses for both teachers and support staff (Law, 2011a, 2011b; News, 2012; NZEI, 2013; Romanos, 2011). Moreover, the Canterbury Primary Principal's Association state that long-lasting anxiety and trauma for schools and children has occurred as a result of this process (E. Murphy, 2016; Radio New Zealand, 2016b) (E. Murphy, 2016; Radio New Zealand, 2016b).

Notwithstanding the fact that challenging child behaviour is always a source of stress for teachers under normal circumstances, the combination of the general effect of the earthquakes on Christchurch residents and the specific stressors relating to school closures and relocations subsequently increased stress levels of affected children, school staff, their families and communities in a mutually reciprocal and interactive way. Consequently, these stressors compounded upon an already present problem, and children's behaviour and emotions were

further negatively affected. This created a setting whereby the relationship of child behaviour to teacher stress needed consideration.

### **1.1.2 Teaching: A stressful occupation**

Johnson and colleagues (S.Johnson et al., 2005) found teachers provided the second worse average score in stress-related outcomes, and sixth lowest levels of job satisfaction when these were assessed across 26 occupations; with the main explanation for these outcomes being the emotional involvement of teachers with students (S.Johnson et al., 2005). The key sources of stress for teachers worldwide primarily include teaching students who display challenging behaviour and lack motivation, and maintaining discipline among students in their classes. Additional sources of stress include high workload, role ambiguity, and poor working conditions and relationships (Kyriacou, 2001).

Consistent with these findings, an exploratory survey conducted in 2016 by Save Our Schools NZ found over 80% of NZ teachers reported they feel stressed or anxious at work half of the time or more, with over 35% reporting they felt this way most of the time. Additionally, approximately 50% of respondents reported students' needs and behaviour as a prevalent cause of stress and anxiety (Kahn & Edgington, 2016). Thus, that teaching is a stressful occupation is well-documented; therefore it is unsurprising that a natural disaster event would exacerbate any existing stress.

### **1.1.3 Child distress and teacher stress**

Psychological distress impacts individuals at any age. It has been found that children in particular have a higher risk of developing mental health issues following a disaster. Examples include childhood traumatic grief (a condition that may develop after the loss of a family member or close friend) and post-traumatic stress disorder (PTSD), whereby an individual may develop sustained changes in emotions, thoughts, and behaviour following exposure to traumatic events (Johnson & Ronan, 2014). A child's reactions to a traumatic event and emotional tensions when they face stressful events following a disaster can be displayed in numerous ways

including re-experiencing of trauma, intrusive thoughts, and hyper-arousal; as well as behavioural issues such as delinquency, increased aggression, disruptive behaviours, withdrawal and avoidance, and decreased academic performance (Erkan, 2009; Fujiwara et al., 2014; V. A. Johnson & Ronan, 2014; Shaw, Espinel, & Shultz, 2007; Y. Wang et al., 2006). Moreover, previous research has found that after earthquake exposure children may experience posttraumatic symptoms such as anxiety, depression, hypervigilance, frequent crying and distractibility as well as psychological effects such as temper tantrums, irritability, sleep disturbances, enuresis and phobias (Jaycox, Morse, Tanielian, & Stein, 2006; Shaw et al., 2007). These effects can persist for many years post-disaster because of a child's less developed capabilities to regulate emotion and cope with the trauma appropriately (Cénat & Derivois, 2015; Goenjian et al., 2011).

Recently in Christchurch, school principals and teachers have expressed concerns regarding the capacity of new entrants (i.e., children in their first year at primary school) to learn and settle in class, as well as delayed language and toileting, all of which can be related to PTS symptoms, a mental health condition associated with conduct and anxiety disorders in children (McCrone, 2014; S. Murphy, 2015; O'Callaghan, 2015; Price, 2014; Radio New Zealand, 2016a; S. Robinson, 2012; Stewart, 2015). Such concerns initiated a study by Liberty and colleagues (Liberty, Tarren-Sweeney, Macfarlane, Basu, & Reid, 2016) that studied 212 five year old children who experienced the Christchurch earthquakes when aged 12-48 months of age, through to the beginning years of primary school (age five to six) with an aim of determining whether the children displayed PTS symptoms as they began primary school. Study data were compared with data from a similar study conducted in 2009 but with children who had not been exposed to a natural disaster. Three years on, the findings were that, compared to the pre-earthquake group, the earthquake-exposed group exhibited clinical PTS symptoms twice as often (Mean = 2.91 vs. 1.98) as well as greater number of high PTS scores (20.7% vs. 8.8%) (Liberty et al., 2016). These results are consistent with previous research looking at the rate of PTS symptoms in older

children and adolescents who have experienced earthquakes or other disasters (Chen & Wu, 2006; Durkin, Khan, Davidson, Zaman, & Stein, 1993; Feo et al., 2014; Jia et al., 2013; Shaw, Applegate, & Schorr, 1996; Trickey, Siddaway, Meiser-Stedman, Serpell, & Field, 2012). As a result, contemporary Christchurch primary school classrooms include a number of children who present with persisting high stress symptoms, which in turn affects teachers' abilities to teach and to cope with children's problems (Liberty et al., 2016).

Such a classroom environment is stressful for teachers. Persistent and/or extensive expression of externalizing behaviour in class by children may lead to psychological distress on the part of teachers. For example, Ferguson, Frost, and Hall (2012) found that depression and anxiety in teachers was significantly influenced by both student behaviour and workload; and low job satisfaction resulted from stress and depression. Additionally, Friedman-Krauss, Raver, Morris, and Jones (2014) found child-teacher conflict and elevated stress levels in teachers increased when child behaviour problems were high and a more negative emotional climate was linked with high levels of job stress. Moreover, workload and psychological distress may derive from role overload and ambiguity (Mirowsky & Ross, 2003). This is something Christchurch teachers may be particularly familiar with as they work additional hours to put together supplemental support programmes for their students and experience increased pressure from Principals to support children's learning; and deal with increased behaviour and learning needs in the classroom, (C. Harris, 2013; O'Callaghan, 2015).

Post earthquake, Christchurch teachers are not only teaching in a stressful environment, but are also on their own journey of recovery from the disaster. Many teachers working in earthquake-affected schools are not only dealing with the effects of stress on their students but are dealing with on-going earthquake stressors of their own, such as those mentioned earlier. Therefore, teachers' wellbeing can be further negatively impacted as they juggle the demands of both work (school) and personal (home) lives. One potential negative effect of these demands,

acting as both a cause and effect of on-going stress, is sleep disruption. Thus the specific link of stress and insomnia is reviewed in the next section.

## **1.2 Insomnia – a brief Review**

A stressful environment such as is commonly experienced in a stressful occupation such as teaching can have numerous effects, one being insomnia, in which an individual experiences problems in the initiation of sleep, early morning awakening, and impaired sleep maintenance, despite adequate opportunity for sleep (American Psychiatric Association, 2013) (American Psychiatric Association, 2013). Moreover, insomnia is further associated with daytime functioning impairments and significant distress (American Psychiatric Association, 2013). Therefore, individuals with insomnia are unable experience sleep that is of an adequate duration or quality to yield refreshment the next morning (Attarian & Perlis, 2010). The threshold distinguishing normal and abnormal sleep is conventionally represented by whether it takes an individual more than 30 minutes to fall asleep and/or if they experience more than 30 minutes of wakefulness after sleep onset (Attarian & Perlis, 2010). Such sleep difficulty must occur at least three times per week, and this must have persisted for more than one month (Roth, 2007). Furthermore, insomnia may be acute, occurring in response to short-term stress and disturbance in life routines (e.g., worry about something; mild illness) or it can be chronic, with general population data showing severe insomnia can last on average four years (Chevalier et al., 1999), with 88.2% still reporting insomnia five years after onset (Mendelson, 1995).

Despite being the most commonly reported and highly prevalent sleep disorder (Ohayon, 2002), insomnia often goes unrecognized and untreated (Morin, 2010). Literature has shown that 30% of individuals report insomnia symptoms, and of these, 15-20% report associated daytime impairment (American Psychiatric Association, 2013). However, using standardised diagnostic criteria, 5-10% of adults meet the criteria for an insomnia diagnosis (American Psychiatric Association, 2013). New Zealand population prevalence estimates are consistent with this international literature. These estimates show 13.0% of New Zealanders between the ages of 20-

59 years report at least one symptom of insomnia often or always, alongside daytime sleepiness (O'Keeffe, Gander, Scott, & Scott, 2012).

### **1.2.1 Epidemiology and Risk Factors of Insomnia**

Although data investigating predisposing factors for insomnia is limited, there are several hypothesized factors including a familial or personal history of insomnia, older age, female gender (Morin & Jarrin, 2013), and work stress (Jansson & Linton, 2006). Women tend to be at a higher risk of developing insomnia compared to men (Leger, Guilleminault, Dreyfus, Delahaye, & Paillard, 2000; Zhang & Wing, 2006). Hypotheses as to why women have higher risk ranges from reporting bias to hormonal changes during their fertile years and during menopause and to a higher prevalence of psychiatric disorders (e.g., depression) in women (M. J. Sateia, 2010). Furthermore, the risk of developing chronic insomnia increases with age (Ohayon, 2002; Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014), which is not surprising, as many factors covary with age, such as pain, medication use, medical illness, and prevalence of other sleep problems (M. J. Sateia, 2010). Work stress is also associated with the development and maintenance of insomnia, including specific perceived stressors such as work demands (Jansson & Linton, 2006). Additionally, low socioeconomic status and unemployment have been found to be highly associated with insomnia (Léger & Bayon, 2010).

Previous research shows high levels of comorbidity of insomnia with multiple psychiatric disorders, particularly anxiety and depression (Goldman-Mellor et al., 2014; Staner, 2010). Data from early studies (D. E. Ford & Kamerow, 1989; Ohayon, Caulet, & Guilleminault, 1997) found, of those presenting with insomnia, over 40% of individuals reported comorbid psychiatric disorders, the majority being anxiety and major depression disorders (D. E. Ford & Kamerow, 1989; Ohayon et al., 1997). These results are similar to those found in more recent studies looking at the association between anxiety and depression and insomnia (Goldman-Mellor et al., 2014; E. Johnson, Roth, & Breslau, 2006; Morphy, Dunn, Lewis, Boardman, &



Croft, 2007; Ohayon & Roth, 2003; Sivertsen et al., 2014; Sivertsen et al., 2012; Strine & Chapman, 2005).

For many years, it was understood that a crucial generating and maintaining factor in the association between psychiatric disorders and insomnia was psychopathology (M. J. Sateia, 2010). Although such an interpretation remains today, several epidemiological studies (Breslau, Roth, Rosenthal, & Andreski, 1996; Riemann & Voderholzer, 2003; Taylor, Lichstein, & Durrence, 2003) suggest an alternate hypothesis, namely that chronic insomnia is a crucial generating and maintaining factor of psychiatric illness (i.e., the causal direction of the association is reversed). In a large population-based multinational study conducted in Europe, Ohayon and Roth (2003) found the first episode of depression was preceded by insomnia 41% of the time, and only 29% of the time did insomnia follow the onset of depression. Similar results were previously reported by Eaton, Badawi, and Melton (1995) and have been confirmed by longitudinal studies (Breslau et al., 1996; Chang, Ford, Mead, Cooper-Patrick, & Klag, 1997). Moreover, research has shown that greater levels of insomnia are associated with more severe depression (Manber & Chambers, 2009).

In terms of anxiety, some studies have found that insomnia precedes anxiety. A review of epidemiological studies by Taylor et al. (2003) found that individuals with insomnia were at greater risk of developing an anxiety disorder (Cohen's  $d = .13-.43$ ) compared to those without insomnia. These results have since been confirmed by later studies (Jansson-Fröjmark & Lindblom, 2008) and in a recent longitudinal study (Jackson, Sztendur, Diamond, Byles, & Bruck, 2014). However, results are mixed as other research has shown insomnia has not been significantly associated with the onset of anxiety disorders. For example, Ohayon and Roth (2003) found insomnia either emerged at the same time (>38%) or after (34%) an anxiety disorder. Similar results were also reported by Johnson, Roth and Breslau (2006).

Additionally, further research has shown that insomnia is associated with various other psychiatric disorders. Previous research shows that compared to controls, individuals with

insomnia are at increased risk of developing panic disorder (Weissman, Greenwald, Niño-Murcia, & Dement, 1997) substance abuse or dependence as a way to self-medicate for sleep (Brower, Aldrich, Robinson, Zucker, & Greden, 2001; Pigeon, 2010; Taylor et al., 2003; Weissman et al., 1997) and hallucinations (Sheaves et al., 2016).

As well as psychiatric illnesses, insomnia shows high comorbidity with many physical illnesses. Significant sleep disturbance is often reported in approximately 50% to 88% of individuals with musculoskeletal pain conditions such as osteoporosis, rheumatoid arthritis, and fibromyalgia (Mai & Buysse, 2008; Morphy et al., 2007; Pigeon, 2010; Sivertsen et al., 2014). Physical fatigue (Kyle, Espie, & Morgan, 2010), obesity (Altevogt & Colten, 2006; Hasler et al., 2005; Sivertsen, Krokstad, Øverland, & Mykletun, 2009), and cardiovascular disease not associated with typical coronary risk factors (Sofi et al., 2014; Spiegelhalder, Scholtes, & Riemann, 2010; Taylor et al., 2007) also show high comorbidity with insomnia, with studies showing insomnia increases the risk of these diseases. Further research also shows associations between insomnia and type II diabetes (Vgontzas et al., 2009), asthma, migraine (Sivertsen et al., 2009; Sivertsen et al., 2014) and increased gastrointestinal, urinary, neurologic and breathing issues (Taylor et al., 2007). It is clear from this research, that insomnia not only has negative impacts psychologically, but physically also.

### **1.2.2 Consequences of Insomnia for daytime functioning**

Numerous studies have shown insomnia negatively impacts individuals, including many areas of daytime functioning showing poorer outcomes on several quality of life measures such as daytime sleepiness, impaired memory and concentration, intrusive thoughts (Baker, Baldwin, & Garner, 2015), reduced ability to complete daily tasks, worsened social functioning, and less enjoyment of interpersonal relationships (Bolge, Doan, Kannan, & Baran, 2009; Orzeł-Gryglewska, 2010; Paine, Gander, Harris, & Reid, 2005; Wilkerson, Boals, & Taylor, 2012). Such daytime consequences can worsen over time, as shown by Komada et al. (2012) in their

longitudinal study and more recently by Ford and colleagues (E. S. Ford, Cunningham, Giles, & Croft, 2015).

Additionally, insomnia also affects individuals in the work place, and D. Henry, McClellan, Rosenthal, Dedrick, and Gosdin (2008) found it was viewed as a barrier to occupational success as it is linked to a higher risk of permanent work disability (e.g., baseline sleep duration and sick leave) (Sivertsen et al., 2009; Sivertsen et al., 2006), and decreased likelihood of future professional progression (e.g., salary increases and promotion) (Kucharczyk, Morgan, & Hall, 2012). Moreover, it has been reported that those with insomnia have a higher likelihood of changing occupations, lower job satisfaction and feelings of mastery and tend to utilize emotion-oriented rather than problem-solving oriented coping strategies (Morin, Rodrigue, & Ivers, 2003).

There is a close association between insomnia and increased cognitive failures in day-to-day activities (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012); ergo individuals with insomnia are at greater risk for occupational errors, mishaps, and work, home and car accidents compared with good sleepers (Daley, Morin, LeBlanc, Gregoire, et al., 2009; Leger, Massuel, Metlaine, & Group, 2006). For example, Leger et al. (2014) reported findings of increased rates of accidents not associated with hypnotic use side effects in those with insomnia compared to those without. Additionally, Kling, McLeod, and Koehoorn (2010) found that women in professional occupations such as teaching and nursing had increased risk of occupational injury due to lack of sleep compared to other occupations. Sleep difficulties and increased risk of work injury may be associated with these occupations as they are often characterized by long hours and high job demands. Extrapolating this to teachers in Christchurch in the post earthquake environment it is likely that there has been, increased risk of work injury is exacerbated due to the extra pressures in the job post-earthquake.

In summary, insomnia is shown to have a wide range of adverse effects on sufferers. Insomnia may result in higher rates of medical consultations, increased use of medical services,

increased medication use, greater work absenteeism and decreased work productivity, and increased industrial and motor-vehicle accident risk (Araújo, Jarrin, Leanza, Vallières, & Morin, 2017; Kyle et al., 2010; Léger, Guilleminault, Bader, Lévy, & Paillard, 2002). Therefore, the worldwide health and economic burden as a result of insomnia is substantial (Daley, Morin, LeBlanc, Grégoire, & Savard, 2009; Léger & Bayon, 2010). To understand insomnia and perchance treat it first requires us to understand normal sleep, the topic of the next section.

### **1.2.3 The physiology of normal sleep**

In contrast to those suffering from insomnia, in normal sleepers, the four sleep stages (Table 1) of the circadian rhythm (“an endogenous rhythm with a period of approximately 24 hours that is entrainable, persists in the absence of external time cues, and is temperature compensated”, Potter et al. (2016), p585) occur overnight in succession in a ‘sleep cycle’, lasting for 90-120 minutes, before repeating approximately three to six times. Two types of sleep occur in this cyclic fashion; Non Rapid Eye Movement (NREM) sleep which represents a continuity of relative depth and accounts for 75-80% of normal sleep, and Rapid Eye Movement (REM) sleep which accounts for 20-25% of normal sleep (Carskadon & Dement, 2011; Stanley, 2005). In normal sleep, a brief awakening (i.e., “prolonged arousal with behavioural impact, including cardiovascular activation”) (Stanley, 2005, p3) is common amid or soon after REM sleep. In good sleep, awakenings are brief, hormones balanced and sleep is easily resumed; however, in disrupted sleep Slow Wave Sleep (SWS) is decreased and stage one sleep increased, meaning insufficient restorative sleep is obtained (Carskadon & Dement, 2011).

Table 1. *Stages of the Sleep Cycle*

Stage	Characteristics
NREM Stage 1 (N1)	Beginning of sleep onset; sleep is easily disrupted; muscle contractions. Lasts on average for 1-7 minutes and occurs as a transitional stage throughout the night.
NREM Stage 2 (N2)	Characterized by specific EEG complexes. At this stage of sleep it is harder to be awakened by external stimuli. Heart rate slows; body temperature drops. Lasts for approximately 10 to 25 minutes.
NREM Stages 3 and 4 (N3)	Transition from light sleep to very deep sleep. Delta sleep (deep sleep), high-voltage slow-wave patterns are seen on EEG indicating restorative sleep. Hard to be awoken at this stage of sleep.
Stage R (REM sleep)	Characterized by episodic bursts of rapid eye-movements during sleep; muscle atonia; altered body temperature; heart rate and respirations increase; and EEG activation. Dreaming is associated with this sleep stage. Arousal threshold is variable during this stage. REM cycles become progressively longer throughout the night.

- NREM = non-rapid eye movement, REM = rapid eye movement. EEG = electroencephalographic activity

*Note:* Information in table obtained from Carskadon and Dement (2011) and Stanley (2005).

#### 1.2.4 Insomnia and the stress system

Previous research has found that the circadian rhythm, and consequently, sleep, is affected after stressful life events, therefore, stress is a risk period for prolonged cognitive and physiological hyperarousal, and thus insomnia (Vedaa et al., 2016). The cognitive hyperarousal model of insomnia (Espie, 2007; Harvey, 2002) posits that a stressed and anxious state evokes excessive negative cognitions about getting adequate sleep, and explains the consequence this has on daytime functioning and health. Autonomic arousal is elicited resulting from activation of the sympathetic nervous system (for instance, by a stressful event), and increased cortical arousal is commonly seen during the sleep onset period in those with insomnia (Levenson, Kay, & Buysse, 2015). Moreover, research shows reduced SWS and increased electroencephalographic (EEG) activity during NREM sleep in those with insomnia (Basta, Chrousos, Vela-Bueno, & Vgontzas, 2007; Cortoos, Verstraeten, & Cluydts, 2006; Hall et al., 2007), which is consistent with a state of hyperarousal.

In terms of physiological arousal, Palagini, Biber, and Riemann (2014) posited that neurobiologic systems that modulate stress-response and sleep-wake regulation are disrupted due to stress and insomnia exposure, therefore enhancing the risk of chronic insomnia. Several studies have provided evidence for physiological hyperarousal in those with insomnia (Bonnet & Arand, 2010; Hall et al., 2007; Riemann et al., 2010). Furthermore, elevated adrenocorticotrophic hormone and cortisol levels that occur during SWS, result in both wakefulness and spontaneous awakenings, both of which are symptoms associated with insomnia (Stanley, 2005). These findings indicate a significant correlation between psychological distress and physiological arousal during sleep.

Additionally, times of high stress and anxiety are metabolically demanding on an individual and the ability of the gastric system to absorb nutrients is hindered. This imposes high nutritional needs that then impact other normal biological activity throughout times of prolonged stress (McCann & Ames, 2009). As a result, the circadian rhythm can be disrupted, thus negatively impacting sleep.

It is clear that stress has a large capacity to disrupt the sleep cycle and promote chronic insomnia. This is of particular relevance to those in Canterbury who have experienced the earthquakes and numerous life stressors that have come with them. As already shown, even under normal circumstances, teaching is a stressful occupation. In addition, previous research also shows that, in comparison to other occupations, teachers experience higher rates of emotional exhaustion, and in turn, increased stress levels (Kuntz, Näswall, & Bockett, 2013). As such, it is likely that teachers working in earthquake-affected schools in Christchurch, who are dealing with ongoing earthquake stressors and teach in classrooms that include a number of highly aroused and reactive children, are under significant daily stress and many may be experiencing the symptoms of insomnia.

### **1.3 Treatments for Insomnia**

#### *Pharmacological Treatment*

It is important for individuals' to seek treatment for insomnia, and to date the pharmacological approach is most widely used. Various pharmacological treatments target numerous aspects of the physiological processes mentioned above (For a review see Ioachimescu & El-Solh, 2012; Szabadi, 2014). Medications most commonly prescribed include hypnotics, benzodiazepines (BZD's), nonbenzodiazepines (non-BZD's), and melatonin receptor agonists (Lie, Tu, Shen, & Wong, 2015; Minkel & Krystal, 2013). BZD's are known for their sedative-hypnotic effects (Minkel & Krystal, 2013) and those approved to treat insomnia include temazepam, triazolam, estazolam, quazepam, and flurazepam; however, off-label BZD's may also be used (e.g., diazepam and lorazepam) (Lie et al., 2015). BZD use increases gamma-aminobutyric acid (GABA) neurotransmitter inhibitory effects in the central nervous system, thereby decreasing sleep onset latency and increasing sleep duration (Cape, 2008); they also suppress slow-wave and REM sleep and prolong stage two sleep (Ebert, Wafford, & Deacon, 2006). Non-BZD's were created in order to decrease adverse effects associated with BZD's; those used for hypnotic use include zolpidem, zalepon, and zopiclone (Lie et al., 2015), of which zopiclone is commonly used in New Zealand to treat insomnia (Kershaw, Vella-Brincat, & McKean, 2011). Non-BZD's elicit decreased slow-wave activity and increased beta and spindle activity in sleep as shown by EEG, thereby increasing the amount of restorative sleep (Ebert et al., 2006).

However, although commonly prescribed, both BZD's and non-BZD's often produce numerous adverse side effects and daytime sedation. Such effects include drowsiness, light headedness, anxiety, anterograde amnesia, impaired memory and balance, cognitive impairment, psychomotor impairment, paradoxical inhibition, increased likelihood of falls, and complex sleep behaviours including sleep-related driving, eating, and sleep walking (Buysse, 2013; Cape, 2008; Krystal, 2010; Lie et al., 2015).

In terms of melatonin (an endogenous hormone involved in circadian rhythms which is produced by the pineal gland), its agonist ramelteon is commonly used to treat insomnia. It is posited that due to its high-affinity for the MT1 receptor, ramelteon regulates drowsiness through weakening wake-promoting signals from the suprachiasmatic nucleus (where sleep-wake rhythms are thought to be controlled) (Minkel & Krystal, 2013; Pigeon, Bishop, & Marcus, 2013; Roehrs & Roth, 2012). Furthermore, melatonin administered externally is posited to accelerate adaptation to sleep phase shifts as well as decrease sleep latency (Deacon & Arendt, 1995). However, ramelteon does not come without side effects; those most commonly reported include headaches, dizziness, nausea and somnolence (Minkel & Krystal, 2013; Lie et al., 2015).

#### *Pharmacological Treatment Efficacy*

Regarding efficacy of pharmacological treatment for chronic insomnia, although short-term efficacy has been established (Buscemi et al., 2007; Smith et al., 2002), long-term efficacy has not (Krystal, 2010; Krystal, Rogers, & Fitzgerald, 2006). Long-term use may be associated with dependence, tolerance, drug-drug interactions, decreased daytime functioning and symptom rebound upon discontinuation, which may be more severe than the original insomnia disorder (Krystal, 2010; Morin & Benca, 2012; M. J. Sateia & Nowell, 2004; Smith et al., 2002). Moreover, studies have not found sustained improvement when pharmacological treatments are discontinued (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Studies on the efficacy and effectiveness of melatonin as a hypnotic are inconclusive, showing a small reduction in sleep latency of 7.2 minutes, and no increase in total sleep time (Buscemi et al., 2007; Schutte-Rodin et al., 2008). Such adverse and/or minimal outcomes of pharmacological treatment have prompted a search for alternative treatments that are beneficial in the long-term.

#### *Cognitive Behavioural Treatment for Insomnia*

One such alternative is cognitive behavioural treatment for insomnia (CBT-I), which uses a multicomponent approach in order to decrease the perpetuating aspects that define insomnia, including irregular sleep-wake schedules, daily napping, excessive time spent in bed, exorbitant



worry and rumination about sleep loss and daytime consequences, and performance anxiety (Morin, 2004; Siebern, Suh, & Nowakowski, 2012). CBT-I is a short-term treatment consisting of approximately four to eight sessions, that encompasses multiple behavioural components (sleep restriction therapy, relaxation training, stimulus control), a cognitive component (restructuring of maladaptive thoughts, beliefs, and attitudes interfering with sleep or that hinder behavioural treatment components), and guidelines that incorporate both cognitive and behavioural components (sleep and sleep hygiene education) (Manber et al., 2011). CBT-I aims to alter cognitions and learned behaviours that perpetuate insomnia, as well as help individuals understand and remove factors contributing to the condition.

### *CBT-I Treatment Efficacy*

CBT-I has proven effectiveness (i.e., produces a positive effect under ordinary day-to-day conditions and aims to enhance external validity while maintaining internal validity) and efficacy (i.e., produces a positive effect under ideal circumstances and aims to enhance internal validity) (Irwin, Cole, & Nicassio, 2006b; Mitchell, Gehrman, Perlis, & Umscheid, 2012; Okajima, Komada, & Inoue, 2011; M. Y. Wang, Wang, & Tsai, 2005), with research showing that it is effective at reducing sleep onset latency ( $d = -0.52$ ) and wake after sleep onset ( $d = -0.64$ ), and increasing sleep efficiency ( $d = -0.99$ ) and quality ( $d = 0.90$ ) (Irwin, Cole, & Nicassio, 2006a). These benefits have been shown to sustain over time compared to the effects of pharmacological treatment, which are often brief (Edinger & Means, 2005; Mitchell et al., 2012; M. Y. Wang et al., 2005). However, despite this, individuals need access to a good therapist and often those diagnosed with insomnia only have limited access to one. This holds true in a post-disaster environment, as there are likely to be few trained mental health professionals available (Suzuki & Kim, 2012), which then creates long waitlists for treatment, something that has been seen in Christchurch post-earthquake (McLennan, 2016). Individuals also need to be willing to put in the time and effort required for sleep practices to change in order for the treatment to be effective (Morin, 2006).

## **1.4 Why Micronutrients Should be Considered for Treating Insomnia**

Recent research into the treatment of mental health disorders has looked at the use of both single-micronutrient and broad-spectrum micronutrients. Micronutrients include all vitamins and minerals required in trace amounts in order to maintain health (Popper, 2014). They are essential for all metabolic processes, and consequently, are essential for physical and mental wellbeing (Kaplan, Rucklidge, Romijn, & McLeod, 2015). In order to maintain physical and mental health and biologic functionality, micronutrient intake must meet nutritionally adequate levels; otherwise deficiencies emerge which can have large impact on both brain development and physical growth (Popper, 2014). Epidemiological research has shown that over the last century, dietary changes in the Western world (Cordain et al., 2005; Crawford et al., 1999), mean that many people are consuming diets significantly lower in micronutrients in comparison to the diets of earlier times (Cordain et al., 2005). With the rise in prevalence of mental health disorders, it is not surprising that a link has been proposed between nutritional intake and mental health.

In order to understand how micronutrients play a role in mental health, it is first important to understand their role in biological functions. Vitamins and minerals play a crucial part in all physiologic, biologic, and chemical processes in the human body (Popper, 2014). Many enzymes require cofactors (coenzymes) so that enzymatic functions within the body can be carried out effectively (Kaplan, Rucklidge, Romijn, & McLeod, 2015; Popper, 2014). Vitamins play a large role in the make-up of cofactors, either being a cofactor (e.g., biotin) or a component of a cofactor (e.g., folate in tetrahydrofolate); whilst minerals can be a structural component of enzymes, operate as cofactors, or switch on enzymes or other proteins (Popper, 2014). As a result, vitamins and minerals are essential for the synthesis and metabolism of many neurotransmitters, which are important chemicals that communicate information throughout the brain and body. For example, pyridoxal 5 phosphate (Vitamin B6) is a cofactor in the synthesis of GABA, serotonin, and epinephrine and norepinephrine, helping to decrease stress-induced

cortisol response; niacinamide (Vitamin B3) helps convert tryptophan to serotonin; methylcobalamin (Vitamin B12) and ascorbic acid (Vitamin C) assist in the synthesis of monoamine neurotransmitters; iron plays a role in the enzyme system that assists in serotonin, dopamine, norepinephrine and epinephrine production and it is also a cofactor assisting synthesis of tyrosine to dopamine; zinc plays a role in almost all areas of metabolism, acting as a cofactor for over 200 enzymes; magnesium is a cofactor that converts carbohydrates and fats to create adenosine triphosphate (ATP), as well as assisting in synthesis of nucleic acids and proteins (Head, Kelly, & 2009; Kaplan, Crawford, Field, & Simpson, 2007; O’Kennedy, 2016).

Furthermore, vitamins and minerals can strengthen and weaken neurotransmitter receptor binding. For example, iron enhances serotonin and dopamine binding to serotonin proteins in the frontal cortex. Moreover, calcium and magnesium play an important role in chemical signalling between cells, whilst cobalamin (Vitamin B12) has an important function in sustaining myelin sheaths, which in turn assists in messages being transmitted between cells (Kaplan et al., 2007). In short, vitamins and minerals play a vital role in normal biological and brain function, meaning they are an avenue worth exploring in the area of mental health and wellbeing generally and in sleep difficulties specifically.

### **1.5 Metabolic Mechanisms, Mental Health, and Sleep**

How then might micronutrients play a role in sleep? Previously it was believed that neurotransmitter imbalances were the primary cause of abnormal mood states, a notion referred to as the catecholamine or biogenic amine hypothesis (Kaplan, Rucklidge, Romijn, & McLeod, 2015). However, more recently it has emerged that this is not the primary cause. In turn, the emerging mental health field of nutritional psychology/psychiatry posits a new model of the biological basis of psychiatric illness which investigates how metabolic mechanisms may play a role in the development of psychiatric problems (Kaplan, Rucklidge, Romijn, & McLeod, 2015). In particular, the role of gastrointestinal inflammation, microbiome alterations and oxidative stress and mitochondrial dysfunction are being investigated (Kaplan, Rucklidge, Romijn, &

McLeod, 2015). Kaplan and colleagues (Kaplan et al., 2007; Kaplan, Rucklidge, Romijn, & McLeod, 2015) have found increasing evidence suggesting these metabolic mechanisms are linked to deficiencies and/or malabsorption of vitamins and trace elements in the expression of some psychiatric symptoms.

### **1.5.1 Inflammation**

Numerous biological mechanisms associate mental health and diet together, and among these, inflammatory processes are hypothesized to play a vital role. Inflammation refers to a non-specific immune response to injury, homeostatic imbalance or infection (N. Simpson & Dinges, 2007). The association between sleep and inflammation is posited to be bi-directional, in that decreased sleep and insomnia can be elicited via stress hormone increases (Krueger, Obál, Fang, Kubota, & Taishi, 2001) and elevated inflammation markers including interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-a) can be increased due to insomnia (Motivala, 2011; N. Simpson & Dinges, 2007). These proinflammatory cytokines (“cell-signalling molecules involved in intracellular communication” Kaplan, Rucklidge, Romijn and McLeod, 2015, p2) both elicit inflammatory responses and are involved in sleep regulation (Motivala, 2011). Cellular and natural immune functioning are altered as a result of both acute and chronic sleep deprivation; however it is not clear what mechanism relates sleep and inflammation (Berk et al., 2013). One suggestion is that lifestyle factors impacting sleep may moderate inflammatory biomarkers through an existing bidirectional relationship that balances host-defence and sleep mechanisms (Berk et al., 2013). Research looking at those with insomnia has found elevated levels of TFN-a, IL-6 and C-reactive protein (CRP) proportional to the duration and quality of sleep (Burgos et al., 2006; Motivala, 2011; Patel et al., 2009; N. Simpson & Dinges, 2007; Vgontzas et al., 2003), and such activation may be a consequence of night-time sympathetic arousal as well as lowered natural immune functioning (Berk et al., 2013).

These IL-6 and CRP elevations are similar to those found in individuals with major depression as compared to non-depressed individuals (Haapakoski, Mathieu, Ebmeier, Alenius,

& Kivimäki, 2015), providing a mechanism by which insomnia may contribute to the etiology of depression. Furthermore, evidence suggests inflammatory system activation occurs in other psychiatric disorders such as schizophrenia (Borovcanin et al., 2012) and bipolar disorder (Hamdani, Tamouza, & Leboyer, 2011). Therefore, if chronic inflammation plays such an important role in the development of mental illness it is important to know its causes, and emerging research points to the role of the gastrointestinal (GI) system.

### **1.5.2 The Microbiome**

Over 90% of our body's cells are microbial cells comprising the human microbiome. The bulk of these microorganisms reside in the gut (microbiota), where they carry out various functions pivotal to health and survival. Microbial cells help to protect the intestinal defence barrier system, digest our food, extract nutrients and help with nutrient synthesis in some cases (Kaplan, Rucklidge, Romijn, & McLeod, 2015; Moos et al., 2016). These microbiota play a pivotal role in the "gut-brain axis", whereby bidirectional communication between the gut and the brain occurs. This communication is reliant on the health of the microorganisms, and imbalance of the gut bacteria, known as dysbiosis, can lead to inflammatory responses thereby contributing to a range of problems in the host including that of mood and behaviour problems via hormone signalling (Berk et al., 2013; Hawrelak & Myers, 2004; Nicholson et al., 2012).

Gut dysbiosis can be a result of numerous causes such as an environment that is too clean, broad-spectrum antibiotic use, poor nutrition, psychological stress (Kaplan, Rucklidge, Romijn, & McLeod, 2015) and sleep difficulties (Reynolds et al., 2016). For example, composition and diversity of gut microbiota can be altered due to psychological stress as shown by animal models in the prenatal period (Golubeva et al., 2015), in early life (Bailey & Coe, 1999; O'Mahony et al., 2009) and in adulthood, where it was found that altered microbiota increased circulating levels of pro-inflammatory cytokines (Bailey et al., 2011), thus increasing the risk of psychiatric problems.

The influence microbiota can have on the host's immune system is substantial, and dysbiosis can produce an inflammatory reaction to toxic material produced by gram-negative bacteria, including Lypopolysaccharide (LPS) (Kaplan, Rucklidge, Romijn, & McLeod, 2015). This inflammatory reaction is evident through increased plasma levels of immunoglobulin (Ig) A and/or M in response to gram-negative bacteria, as seen in those with clinical depression (Kaplan, Rucklidge, Romijn, & McLeod, 2015; Maes, Kubera, Leunis, & Berk, 2012). Such a response suggests that bacterial translocation (whereby bacteria transfers from the inside of the intestinal tract to the outside) plays a part in the development of inflammatory responses in mental illness such as depression (Berk et al., 2013). Bacterial translocation occurs when the mucosal barrier across the gut wall becomes permeable as a result of loosening of the tight junction barrier. This allows gram-negative bacteria to pass outside of the intestinal tract, thus triggering inflammatory pathway activation via cells in the immune system that are not readily prepared against the LPS encased within gram-negative bacteria (Berk et al., 2013; Kaplan, Rucklidge, Romijn, & McLeod, 2015); consequently, brain function can be affected. Evidently, there is a strong relationship between dysbiosis and inflammation; however, there are other factors that may cause inflammation, such as oxidative stress.

### **1.5.3 Oxidative Stress**

Oxidative stress (OS) is an important mechanism to consider when investigating potential causes of inflammation. Oxygen is an essential factor of life, and it is important to note that pro-inflammatory cells exist in normal metabolic function and help fight off infection. Normal metabolic functioning creates molecules with unpaired electrons containing oxygen, known as reactive oxygen species (ROS) (Kaplan, Rucklidge, Romijn, & McLeod, 2015). These free radicals are essential for cellular signalling, mitosis and physiological immunological responses; however, due to differing oxidative strengths, damage to DNA, RNA, cellular proteins, carbohydrates, lipids and nucleic acids is possible (Ng, Berk, Dean, & Bush, 2008). In normal conditions, these negative effects are controlled via certain intrinsic biological processes (e.g.,

antioxidant production) (Kaplan, Rucklidge, Romijn, & McLeod, 2015; Ng et al., 2008).

Increased OS occurs when ROS levels are elevated and antioxidant production is decreased, which in turn, can contribute to the pathogenesis of mental health issues (Kaplan, Rucklidge, Romijn, & McLeod, 2015).

Biomarkers including superoxide dismutase (SOD – an antioxidant enzyme that decreases cell damage via ROS detoxification), nitric oxide activity and thiobarbituric acid reactive substances (TBARS – a byproduct of lipid peroxidation) are often employed to detect OS (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Altered levels of these biomarkers have been found in those with depression (Maes, Galecki, Chang, & Berk, 2011), bipolar disorder (Brown, Andreazza, & Young, 2014), Attention-Deficit/Hyperactivity Disorder (ADHD) (Ceylan, Sener, Bayraktar, & Kavutcu, 2012), and schizophrenia (Ciobica, Padurariu, Dobrin, Stefanescu, & Dobrin, 2011). Lack of adequate sleep is known to have a worsening effect on these conditions. Previous research has found significantly increased malondialdehyde (MDA – end product of lipid peroxidation) and decreased glutathione peroxidase (GSH-Px – antioxidant enzyme containing selenium) levels in insomnia patients relative to healthy controls, indicating that sleep deprivation can result in greater OS (Hamdani et al., 2011) and decreased antioxidant factors (GSH-Px), therefore suggesting that sleep plays an important role in OS reduction (Gulec et al., 2012; Tsaluchidu, Cocchi, Tonello, & Puri, 2008). Therefore if OS is a causal factor of inflammation and plays an important role in the pathogenesis of mental disorders, it is important to determine what influences oxidative stress in the first place, and recent research is finding growing evidence that mitochondrial dysfunction may play a vital role.

#### **1.5.4 Mitochondrial Impairment**

Through evolution humans have developed cellular organelles called mitochondria that aid in managing inflammation and OS. Mitochondria are energy producing intracellular organelles present in large numbers in virtually all human cells. The energy supplied comes in the form of adenosine triphosphate (ATP). ATP production starts with carbohydrates, fats and

proteins being broken down (a process that begins in the gut under the influence of the microbiome) resulting in the production of acetyl coenzyme-A, which is then oxidised (electrons are removed) in the Krebs's cycle. These electrons are then donated to the electron transport chain (ETC), where they then transfer through a sequence of chemical reactions which supply a stable environment for ATP production. In order for the Krebs's cycle and ETC to function optimally many coenzymes are needed, many synthesized from dietary nutrients (Kaplan, Rucklidge, Romijn, & McLeod, 2015).

Apart from the nucleus, mitochondria are the only cell organelle containing DNA (mtDNA), and are thereby vulnerable to ROS induced damage due to their close proximity to the ETC. Mitochondrial dysfunction resulting from mtDNA mutation and OS negatively impacts brain function through reduction of ATP. The brain requires ATP produced by mitochondria to function optimally, and uses approximately 20% of all energy produced by mitochondria. Most of this energy facilitates excitatory neurotransmission in the cortex, where the amino acid glutamate as well as other antioxidants, play an important role to help protect the brain from oxidative damage. Therefore, reduction in ATP availability negatively impacts brain function, and research posits that this may be a causal factor of some mental illness, a further idea worth considering (Kaplan, Rucklidge, Romijn, & McLeod, 2015).

In terms of sleep disorders, it is reasonable to assume that mitochondrial dysfunction may occur as a result of sleep deprivation due to the crucial role sleep plays in OS (Gulec et al., 2012). Sleep may act as a protection against oxidative damage, and it is posited that ROS levels increase during wakefulness and are removed during sleep. Sleep deprivation decreases the chance of free radical removal, meaning there is increased risk of ROS-induced damage in the ETC of mitochondria which may lead to mitochondrial disease. For example, Frau-Méndez et al. (2017) found that complex I, II, III, IV and V levels (i.e., ETC complexes that aid in ATP production) were decreased in a human sample of individuals with fatal familial insomnia, with the authors concluding that severe mitochondrial impairment contributes to the course of FFI as



a result of sleep deprivation, which in turn leads to increased ROS production, thereby resulting in oxidative damage to DNA, proteins and lipids. Moreover, further research in humans has found reduced sleep efficiency and duration is associated with lowered mtDNA copies within 30 monozygotic twin pairs (Wrede et al., 2015), suggesting mitochondrial energy production is impaired, and factors such as OS are likely to contribute to this dysfunction.

Together, these findings suggest that mitochondrial dysfunction may play a role, potentially and important one, in the development of sleep disorders; however, causation cannot be determined. Mitochondrial dysfunction can be significantly influenced by nutrition; however, it is difficult to determine specific nutrients that optimize mitochondrial functioning (Kaplan et al., 2015b). When the mitochondrial functioning process are looked at as a whole, most vitamins, minerals, amino acids, and essential fatty acids play a role (Kaplan, Rucklidge, Romijn, & McLeod, 2015); and as inflammation, gut dysbiosis, oxidative stress and mitochondrial functioning are all interrelated, it is plausible that use of multiple nutrients may play a role in the restoration of the impaired metabolic mechanisms seen in those with sleep disturbances and psychiatric illness.

## **1.6 Association between micronutrient deficiencies and sleep**

Given the evidence reviewed above there has recently been a growing interest in the association between sleep and nutrition, albeit often speculative; however, the impact that micronutrients in particular may have on sleep has received little attention. Previous experimental studies have posited that sleep regulation neurotransmitters and nerve-signaling chemicals such as N-methyl-D-aspartate (NMDA) (Sowa-Kućma et al., 2008), serotonin (Ursin, 2002), and melatonin secretion (Honma, Kohsaka, Fukuda, Morita, & Honma, 1992) may be impacted by micronutrients, which has further lead researchers to investigate the relationship between sleep and micronutrients in both observational and clinical studies.

Although research on the relationship between micronutrient intake and insomnia specifically is scarce, several observational studies have identified an association between

micronutrient deficiencies and sleep patterns. In terms of B vitamins, previous research has found that lower vitamin B12 and B6 status in young women was associated with a later midpoint of sleep (Sato-Mito, Shibata, Sasaki, & Sato, 2011), and Zadeh and Begum (2011) found that in a study of 87 adults, those with insomnia displayed deficiencies in thiamine (Cohen's  $d = -0.74$ ), vitamin B12 ( $d = -0.74$ ) and B9 (folic acid) ( $d = -0.73$ ) in comparison to normal sleepers, a significant result. Further significant associations were found between lower levels of vitamins B2 ( $d = -0.75$ ) and B3 ( $d = -0.72$ ) and insomnia compared to those without (Zadeh & Begum, 2011). When looking at sleep quality and duration in a cross-sectional sample of 2,459 adults, Beydoun et al. (2014) found that, those with lower intakes of vitamin B12 and folic acid reported shorter sleep duration compared to normal sleepers. Reports of both vitamin B12 and vitamin B9 deficiencies is not surprising as a secondary deficiency in folic acid can occur as a result of vitamin B12 deficiency. This is because both these vitamins are involved in monoamine neurotransmitter synthesis, and vitamin B12 plays a role in the metabolism of folate (Kaplan et al., 2007).

Several studies have also reported on the association between vitamin D (25(OH)D) deficiencies and sleep. For example, treatment seekers at a sleep medicine clinic displayed significantly greater levels of vitamin D deficiency compared to clinically normal sleepers (54% vs 29.5%) (McCarty et al., 2013). Several cross-sectional studies consistently found that short sleep duration and lower sleep efficiency were significantly associated with lower levels of serum 25(OH)D in older adults compared to normal sleepers (Bertisch, Sillau, De Boer, Szklo, & Redline, 2015; Kim, Chang, Kim, & Kang, 2014; Massa et al., 2015). Furthermore, in a cross-sectional sample of 6139 adults aged over 20 years who were on average vitamin D deficient, lower 25(OH)D serum levels were statistically significantly associated with greater sleep latency (Shiue, 2013).

In terms of mineral deficiencies and sleep, a nationally representative sample of 5587 adults disclosed that very short sleep (<5 hours) was statistically significantly associated with

lower intake of magnesium, phosphorous, iron, zinc and selenium in comparison to normal sleepers (Grandner, Jackson, Gerstner, & Knutson, 2013). Lower intake of iron has also been found to be significantly associated with insomnia ( $d = -0.72$ ) (Zadeh and Begum, 2011). Moreover, Sato-Mito et al. (2011) found that later sleep midpoint (the halfway time point between sleep onset and offset) was significantly associated with lower potassium ( $d = 4.17$ ), magnesium ( $d = 5.00$ ), calcium ( $d = 6.00$ ) and zinc ( $d = 4.00$ ) intake in female students aged 18-20 years. Additionally, in relation to sleep efficiency and duration, a cross-sectional sample of 126 women aged 21 – 72 years showed that lower sleep efficiency and short sleep duration was associated with lower zinc:copper ratio serum levels ( $d = -3.67$ ) and lower zinc levels ( $d = -1.29$ ) (Song, Kim, & Jung, 2012).

### **1.7 Effect of single micronutrient interventions on sleep patterns**

In past research the focus has been on investigating the effect of one vitamin and mineral at a time on the treatment of psychiatric illness (Kaplan et al., 2007), and given the association between deficient micronutrient status and poor sleep, a small number of experimental trials have investigated the effect of single nutrient supplementation on sleep. Randomized controlled trials (RCT) investigating the effect of vitamin B12 supplementation on poor sleep have found mixed results. An experimental trial of 9 healthy males between 20-28 years of age found no significant differences in both the duration and timing of sleep after four weeks supplementation of vitamin B12 (methylcobalamin - 3mg/d) compared to placebo (Honma et al., 1992). Okawa et al. (1997) found similar results in an RCT whereby no significant differences were found in sleep duration and daytime sleepiness in a sample of 50 individuals aged 13-55 years with delayed sleep phase syndrome after administration of methylcobalamin (3mg/day) for four weeks compared to placebo. An RCT investigating the dose effect of 8-week methylcobalamin supplementation in 48 individuals with sleep-wake rhythm disorders found a statistically significant improvement in delayed sleep phase and longer sleep-wake cycles after four weeks between the high dose group (6mg/d) and low dose control group (0.03mg/d); however, after 8

weeks of supplementation this difference was no longer significant (Takahashi et al., 1999). In contrast, Mayer and colleagues (1996) (Mayer, Kroger, & Meier-Ewert, 1996) found that 10 healthy adults receiving methylcobalamin (3mg/d) supplementation for 14 days showed significant improvements in night sleep and daytime alertness and concentration in comparison to adults receiving cyanocobalamin (3mg/d).

Previous RCTs have, however, found evidence to suggest vitamin B1 supplementation positively impacts sleep. For example, Smidt, Cremin, Grivetti, and Clifford (1991) reported improvement in sleep patterns and significant decrease in daytime fatigue ( $d = 5.15$ ) in a sample of 80 elderly women after vitamin B1 supplementation (10mg/d) for six weeks compared to placebo. Furthermore, Wilkinson, Hanger, Elmslie, George, and Sainsbury (1997) found vitamin B1 supplementation (10mg/d) for three months elicited a positive effect on sleep and energy in 76 deficient elderly individuals compared to control; however, these results did not reach statistical significance. In terms of vitamin B3, statistically significant increases in REM sleep and increased sleep efficiency were found in a small study of both normal sleepers and those with insomnia after vitamin B3 supplementation (500-3000mg/d) for three weeks (C. Robinson, Pegram, Hyde, Beaton, & Smythies, 1977). When looking at vitamin D in an uncontrolled trial, Huang, Shah, Long, Crankshaw, and Tangpricha (2013) reported significantly improved sleep duration ( $d = -0.42$ ) and latency ( $d = 0.19$ ) after vitamin D supplementation in 28 veterans with vitamin D deficiency or insufficiency. Moreover, another uncontrolled trial of 1500 individuals with diverse sleep disorders also showed reduced sleeping difficulties after vitamin D supplementation (Gominak & Stumpf, 2012). However, these findings are to be considered with caution as the methods and analyses for this trial are not yet published.

Previous research has also looked into the effect of mineral supplementation on poor sleep status. An RCT by Abbasi et al. (2012) demonstrated statistically significant improvements in sleep time ( $d = 0.42$ ), sleep efficiency ( $d = 0.81$ ), sleep onset latency ( $d = -0.95$ ), and early morning awakening ( $d = -0.53$ ), in 43 older adults compared to controls after 8-week magnesium

supplementation (500mg/d). In contrast, Nielsen, Johnson, and Zeng (2010) found that despite 96 adults with poor sleep quality showing decreased Pittsburgh Sleep Quality Index (PSQI) scores, no statistically significant difference was found between the 7-week magnesium supplementation group and placebo group. When investigating the effects of potassium supplementation on sleep quality in a crossover RCT of young men, Drennan, Kripke, Klemfuss, and Moore (1991) found that sleep efficiency was statistically significantly improved ( $d = -0.53$ ) and sleep latency and sleep interval (time in bed) were statistically significantly reduced in both sleep log and actigraph measures in those receiving potassium supplementation (96meq/day) compared to controls.

When looking at these findings as a whole, it is important to consider that the treatment durations varied greatly, from as little as one week to 12 weeks. Additionally, doses used were also low which may have further impacted study outcomes. Therefore, while some of these studies provide some evidence of efficacy in treating sleeping difficulties with single nutrients, the findings are not consistent and are largely modest, suggesting that single nutrient interventions are not reliable treatments for insomnia. Given that micronutrients work best when they are properly balanced together and that they play a coordinated role in optimal brain functioning, studying a broad range of multiple nutrients simultaneously for the treatment of mental health disorders has become more accepted (Kaplan, Rucklidge, Romijn, & McLeod, 2015).

## **1.8 The effect of multnutrient interventions on mental health**

A growing body of research is demonstrating the effectiveness of multnutrient treatment for a variety of mental health conditions including mood, anxiety, stress and sleep. This approach is proving to have greater beneficial effects compared to one nutrient alone.

### **1.8.1 Mood**

Several RCTs have shown positive effects of multiple micronutrients on mood in adults. E. Harris et al. (2011) conducted an 8-week double-blind RCT on 50 healthy older men (50-69

years), and found those receiving a multivitamin (Swisse Men's Ultivite) experienced improved mood compared to placebo ( $d = 0.39 - 0.53$ ). Sarris et al. (2012) sought to extend these particular findings in a 16-week double-blind RCT of 114 healthy adults, and found those taking a multivitamin showed statistically significant improvements in both mood and energy levels compared to placebo. Additionally, Lewis et al. (2012) conducted a double-blind RCT involving 60 adults diagnosed with depression and found those receiving a vitamin B complex formula (i.e., with a range of B vitamins) compared to placebo displayed statistically significantly more improvement as measured by the Beck Depression Inventory (BDI).

### **1.8.2 Anxiety**

Numerous studies have looked at the effect of micronutrients on stress and anxiety, showing positive results. Five RCT's have examined the effects high dose B vitamins have on both stressed and healthy adults (Rucklidge & Kaplan, 2013), with all showing positive effects. Four of these were double-blind RCTs with similar treatment lengths of 28 days (Carroll, Ring, Suter, & Willemsen, 2000), 30 days (Schlebusch et al., 2000), 33 days (Kennedy et al., 2010), and 90 days (Stough et al., 2011). These studies showed that 80 healthy male volunteers (18-42 years) (Carroll et al., 2000), 300 highly stressed adults (18-65 years) (Schlebusch et al., 2000), 215 males (30-55 years) (Kennedy et al., 2010) and 60 adults (Stough et al., 2011) taking an over-the-counter B vitamin complex were less anxious, stressed, and depressed on average than those on placebo. Berocca (a dissolvable tablet containing vitamins B and C) was used in three of these trials (Carroll et al., 2000; Kennedy et al., 2010; Schlebusch et al., 2000), and another high dose vitamin B formula (Blackmores executive B Active) was used in the fourth (Stough et al., 2011). The fifth unblinded RCT (Rucklidge et al., 2012) will be discussed below.

### **1.8.3 Insomnia**

As previously stated, little attention has been paid to the impact micronutrients have on sleep. However, Rondonelli and colleagues (Rondonelli et al., 2011) in a double-blind RCT investigated the effect of 8-week nightly administration of magnesium (225mg/d), zinc

(11.25mg) and melatonin (5mg) on insomnia in 43 older adults ( $\geq 70$  years). It was found that supplementation compared to placebo significantly improved sleep quality as measured by the PSQI (Cohen's  $d = -1.92$ ), and statically significant improvements were also seen in sleep onset latency, hangover on awakening from sleep, and alertness the next morning (Rondanelli et al., 2011).

## **1.9 Literature on EMPowerplus**

These micronutrient studies demonstrate the effectiveness of using a wider range of micronutrients in the treatment of some mental health conditions. The most studied broad-spectrum micronutrient formula studied to date is called EMPowerplus (EMP+; there are similar formulations with other names), consisting of 36 various vitamins, minerals, amino acids, and antioxidants (see Appendix A). EMP+ has been shown to be effective in a wide range of psychiatric conditions including mood, Attention-Deficit/Hyperactivity Disorder (ADHD), anxiety and stress, and obsessive compulsive disorder (OCD) in both adults and children (Rucklidge & Kaplan, 2013).

### **1.9.1 Mood**

All four publications of open-label trials (Frazier, Fristad, & Arnold, 2012; Kaplan et al., 2001; Popper, 2001; Simmons, 2003) using EMP+ have shown significant reduction in bipolar symptoms in adults and children with bipolar disorder. Kaplan and colleagues (2001) demonstrated a significant reduction in bipolar symptoms as measured by the Hamilton Rating Scale for Depression, Brief Psychiatric Rating Scale and Young Mania Rating Scale measures (Cohen's  $d > .80$ ) in 11 adults (19-46 years) after six months of supplementation. Popper (2001) found that, of 22 patients (10 adults, nine adolescents, three children), 19 individuals displayed clinician evaluated improvements in bipolar symptoms (10 clinical, seven mild, two moderate). In a similar naturalistic trial Simmons (2003) reported that of 19 patients (18-68 years), 16 individuals displayed clinician-evaluated improvements in bipolar symptoms (12 clinical, three mild, one moderate). In all cases, clinically significant symptom improvement was retained over

at least a 6-month period, and less medication was required to maintain symptom control ( $d > .80$ ). An ABAB reversal design case study on a female adult (21 years) diagnosed with bipolar disorder II and ADHD (Rucklidge & Harrison, 2010) reported significant clinical improvement in mood and ADHD symptoms after 8-week supplementation of EMP+, and at 1-year follow-up was reported to be in remission of all psychiatric symptoms. Furthermore, a database analyses on adults ( $N = 358$ ) (Gately & Kaplan, 2009) with bipolar disorder found that taking EMP+ improved bipolar symptoms significantly, with an effect size of Cohen's  $d = 0.76$ . These improvements were sustained over six months, and were related to increased micronutrient dosage and medication reduction (Gately & Kaplan, 2009; Kaplan, Rucklidge, Romijn, & McLeod, 2015).

### **1.9.2 Attention-Deficit/Hyperactivity Disorder**

In terms of ADHD, broad-spectrum micronutrient supplementation has been found to be effective in adults. An open label 8-week trial of EMP+ with a 2-month natural extension found significant improvement (Cohen's  $d = 0.66 - 2.55$ ) in all outcome measures (hyperactivity/impulsivity, inattention, quality of life, mood, anxiety and stress) in 14 medication-free adults (nine men, five women; 18-55 years) diagnosed with ADHD and severe mood dysregulation (Rucklidge, Taylor, & Whitehead, 2011). These improvements were maintained at follow-up in those continuing to take EMP+. Additionally, a recent placebo-controlled 8-week RCT (Rucklidge, Frampton, Gorman, & Boggis, 2014a) demonstrated significant improvements in ADHD symptoms and general functioning after EMP+ supplementation compared to placebo in 80 adults ( $d = 0.46 - 0.67$ ). Moreover, these changes were sustained at 1-year follow up compared to baseline in adults ( $d = 0.39 - 0.62$ ) (Rucklidge, Frampton, Gorman, & Boggis, 2014b). Cohen's  $d$  effect sizes for these studies fell in the moderate to large range (0.46 to  $> 0.80$ ), therefore increasing confidence in the positive effect micronutrients have on ADHD symptom improvement.



### **1.9.3 Obsessive Compulsive Disorder**

Rucklidge (2009) demonstrated in an ABAB design the effectiveness of EMP+ on OCD in a case study of an 18-year old male, who previously underwent unsuccessful psychological treatment. The subject underwent EMP+ supplementation for 8 weeks, which yielded significant improvement in anxiety; however, symptoms of depression were still relatively high. After an 8-week withdrawal from treatment, anxiety, obsession and depression scores increased significantly. EMP+ supplementation was reintroduced yielding improvements after just 12 days, and by four weeks OCD symptoms were in remission. These improvements were maintained six months later, with further reduction in depression symptoms (Rucklidge, 2009).

### **1.9.4 Anxiety in a Post-disaster Context**

The Christchurch earthquakes have provided researchers the opportunity to demonstrate the impact micronutrients can have on anxiety, stress and resilience in a post-disaster context. The fifth unblinded RCT (Rucklidge et al., 2012) mentioned above investigated the effect of micronutrient formulas, CNE (an equivalent of EMP+) high dose (8 capsules) and CNE low dose (4 capsules) and Berocca (one tablet per day), on stress, anxiety, and PTSD symptoms in 84 adults (>18 years) following the Christchurch 6.3 earthquake after shock in February, 2011. Results found that all groups yielded statistically significant improvement in all symptoms; however, those on the high dose CNE with a broader spectrum of minerals improved the most. This result was sustained at the one year naturalistic follow-up (Cohen's  $d = 0.69-1.31$ ) (Rucklidge et al., 2014). Kaplan, Rucklidge, Romijn, and Dolph (2015) replicated this research in an RCT of 56 Canadian adults (23-66 years) following a severe flood in the city of Calgary and environs. After six-week supplementation by either EMP+ (N=18), a B-complex formula (N=17) or Vitamin D (N=21), significant improvement was found in stress and anxiety in those receiving the B-complex or EMP+ formulas compared to those receiving vitamin D alone as measured by the Depression, Anxiety, and Stress Scale (DASS-42) ( $d = 0.76 - 1.08$ ).

Additionally, Rucklidge and Blampied (2011) found that 17 adults taking EMP+ with pre-existing vulnerabilities (ADHD) and facing the stress accompanying the initial Christchurch earthquake displayed greater resilience and therefore significantly less anxiety and stress as measured by the DASS compared to 16 controls ( $d = 0.69$ ). Therefore, these findings provide evidence that vitamins and minerals may be strongly involved in regulation of the stress response, specifically in a post-disaster context.

### **1.9.5 Insomnia**

In terms of insomnia, recent research has emerged showing the significant positive effects of micronutrients on insomnia in adults (Lothian, Blampied, & Rucklidge, 2016). Lothian et al. (2016) have shown that use of a broad-spectrum micronutrient, Daily Self Defense (DSD) ([www.hardynutritionals.com](http://www.hardynutritionals.com)) (a revision of EMP+ developed for general population use), over an 8-week period in an open-label multiple baseline design yielded improvements in insomnia symptoms ( $d = 3.45$ ), stress ( $d = 2.53$ ), anxiety ( $d = 1.36$ ) and mood ( $d = 1.33$ ), with all adult participants displaying reliable positive change. Such results show that alleviation of insomnia symptoms with micronutrients restores sleep after stressful life events through adequate nutrition. Considering the DASS measure, micronutrients had the greatest effect on stress, however, despite the association between stress and sleep, insomnia symptoms improved before stress during the intervention. This meant that insomnia symptom improvements were not in response to stress reduction and therefore stress did not directly mediate sleep improvement.

In summary, EMP+ (and related formulations) has been investigated for numerous mental health conditions in adults, including those associated with stress, and shows promising outcomes in the treatment of these conditions. In particular, given the evidence that nutritional supplementation has beneficial effects on stress and sleep, a trial of micronutrients with teachers experiencing stress and insomnia in the post-earthquake environment in Christchurch seems warranted.

### **1.10 Aims and Hypotheses**

The aim of the current study is to investigate the effect of a broad-spectrum micronutrient formula, EMP+, on chronic insomnia in teachers. As Lothian et al. (2016) found positive results using a broad-spectrum micronutrient formula to treat insomnia in adults, the following research endeavours to determine whether this positive effect can be replicated in teachers working in schools that have been impacted by the Christchurch earthquakes, whilst improving on the methodology of Lothian et al. (2016) through use of a placebo. Such research is important because it is essential that teachers are able to function optimally both cognitively and emotionally in order to not only improve their own mental and physical wellbeing, but also to optimize the children's learning, and teacher's ability to cope with and help highly aroused and chronically distressed children.

It is hypothesised that this study will find the following:

1. The micronutrient formula will be associated with improvements in insomnia symptoms relative to placebo.
2. The micronutrient formula will also be associated with improvements in stress and in anxiety and mood if relevant, relative to placebo.
3. The micronutrient formula will also be associated with improvement in emotional exhaustion and depersonalisation if relevant.
4. The micronutrient intervention will have greater effect than placebo on primary measures of insomnia and wellbeing.
5. Improvements will be maintained over the follow-up period if participants remain on the micronutrient formula, and improvements will be maintained at a lower level for those who discontinue.
6. The micronutrient formula will not be associated with significant side effects and if present, these will be minor and transitory.

## **2. Method**

### **2.1 Participants**

Between September and early October 2016 teachers from selected schools in Christchurch, New Zealand, were, with their Principal's permission, approached via email to participate in the study, with the email including Information and FAQ sheets (see Appendix B). Those approached were teachers from primary and secondary schools substantively affected by the 2010 and 2011 earthquakes, including those from the east and coastal areas of the city. This particular sample was selected because many teachers in these schools were likely to have experienced increased stress (including symptoms of insomnia), with stress arising in particular from the presence in their classes of numbers of children with emotion regulation difficulties and high levels of chronic arousal.

The Information Sheet contained comprehensive information about the study as well as contact details of the researchers. Potential participants were directed to a website ([www.bit.ly/insomniaandnutrition](http://www.bit.ly/insomniaandnutrition)), with a link to an online screening questionnaire developed using Qualtrics software ([www.qualtrics.com](http://www.qualtrics.com)), which contained demographic information questions and screening questions about sleep and associated psychological measures (e.g., depression, anxiety and stress) (see Appendix C). At the end of the questionnaire, teachers were thanked for completing the screening and were informed that the researcher would be in contact about their eligibility as soon as possible. Potential participants not meeting inclusion criteria cut-off scores, or selecting an answer set as part of exclusion criteria (see below), were provided with information on the study product and how to obtain it themselves, and directed to local services available for both sleep and mental health care.

#### **2.1.1 Inclusion and exclusion criteria**

In order to be considered eligible for the study, teachers were required to meet the criteria for insomnia as measured by the Pittsburgh Insomnia Symptom Questionnaire (PISQ, for explanation see below in Measures). Therefore they must have trouble falling asleep or

maintaining sleep at least three or four times a week, and this must have occurred for at least 4 weeks. They also must rate their lack of sleep as affecting their daily functioning at least “quite a bit”. In order to determine the severity of insomnia, the Pittsburgh Insomnia Rating Scale- 20 (PIRS-20, for explanation see below in Measures) was employed, and participants were included if their score was above the clinical cut-off of 20, identifying people with at least mild to moderate insomnia. Teachers had to be Registered and have at least two years experience working full time, live in Canterbury, be at least 18 years of age, have access to a computer and home internet connection, and have been psychiatric and/or sleep medication-free for at least 4 weeks prior to commencing the study.

Exclusion factors assessed by self-report included (a) any neurological disorder involving CNS function or the brain (e.g., narcolepsy, epilepsy, Multiple Sclerosis); (b) sleep apnoea; (c) any serious medical disorder requiring treatment during the trial; (d) any known abnormality of mineral metabolism (e) pregnant/breastfeeding, or intending to have children in the near future; (f) parent of a young child under two; and (g) have consumed an oral antibiotic in previous six weeks.

The study protocol was approved by the University of Canterbury Human Ethics Committee, and the trial was registered prospectively with the Australian New Zealand Clinical Trials Registry (ACTRN12616001026415).

### **2.1.2 Final Sample**

Of 42 teachers who completed the online screening questionnaire, 25 either did not meet the PISQ and PIRS cut-off scores for insomnia or were identified to currently be taking psychiatric/sleep medication. This left 17 teachers who were experiencing the symptoms of insomnia and were not taking any psychiatric/sleep medication. Of the 17 teachers, 11 taught at primary schools and 6 taught at secondary schools. One participant indicated they had a past anxiety disorder that was no longer current and no participants disclosed that they had a current

psychiatric disorder. All 17 eligible participants entered and completed the trial (Figure 1 demonstrates participant flow throughout the study).

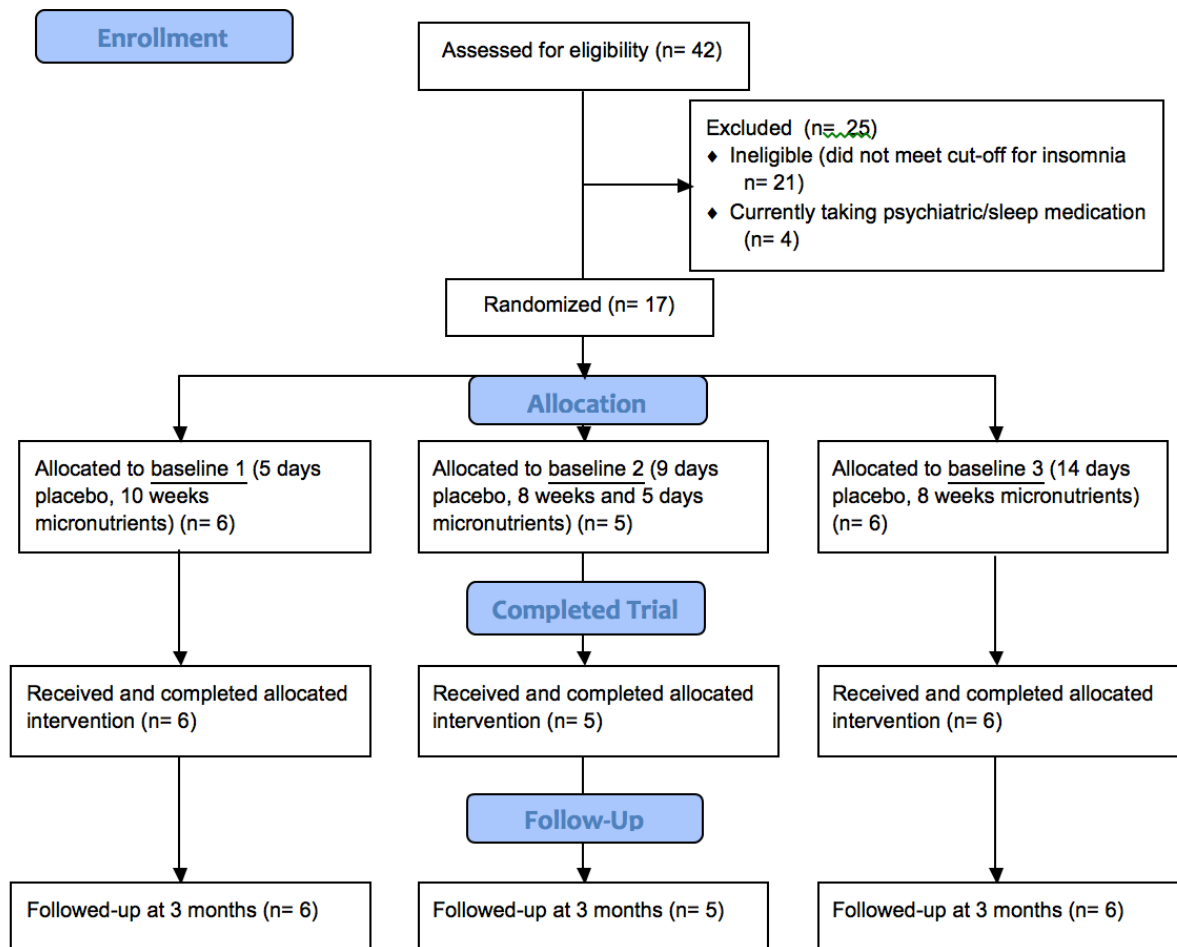


Figure 1. CONSORT flow diagram

## 2.2 Measures

Four of the measures listed below were completed online by the participants using Qualtrics both at baseline, throughout the intervention and at follow-up. The fifth measure (the Consensus Sleep Diary-Morning) was completed in hard copy format at baseline, throughout the intervention and at follow-up.

### 2.2.1 Demographic Information

At screening, participants indicated their date of birth, ethnicity, highest educational qualification (measured on a five-point scale from 1 “university bursary or scholarship” to 4

“university degree” and an option for “other”), and household income (measured on a five-point scale from 1 “less than \$20,000” to 5 more than \$80,000”).

### **2.2.2 Primary outcome measures**

#### *The Pittsburgh Insomnia Symptom Questionnaire (PISQ)*

The PISQ was completed once at initial screening and aims to identify insomnia through a 13-item self-report questionnaire that incorporates both the DSM-IV criteria for insomnia as well as those of the International Classification of Sleep Disorders (Okun et al., 2009). The first five questions of the PISQ aim to determine the frequency of individual’s complaints regarding difficulty in ability to initiate or maintain sleep, or not feeling refreshed or restored after sleep due to poor sleep quality, as well as symptom duration, and the remaining eight questions assess the severity of daytime correlates of sleep complaints (Okun et al., 2009). In order to evaluate the presence, frequency, and/or severity of a complaint in questions 1-5, the items are presented as multiple-choice questions on an ordinal scale of 0 = never to 5 = always. This is followed by open-ended questions that allow individuals to indicate whether the duration of the problem has persisted for weeks, months, or years. Questions 6-13 are scored similarly on an ordinal scale from 0-4 where 0 = not at all to 4 = extremely (Okun et al., 2009).

#### *Pittsburgh Insomnia Rating Scale - 20 (PIRS-20)*

The PIRS-20 is a shorter version of the 65-item PIRS, that focuses on sleep and wake symptoms as they occurred in the week prior to completion of the instrument. The 20 items were chosen from the original study of insomnia patients and control subjects, and item selection was based upon their classical and item response characteristics, to include daytime and night-time items, excluding influence of depressive and anxiety symptomatology (Michael J. Sateia & Buysse, 2010). The PIRS-20 includes 12 items examining the intensity of distress related to night-time and daytime symptoms of insomnia on a scale from 0-3 where 0 = *not at all bothered* and 3 = *severely bothered*; four items also scored on a 0-3 scale assessing quantitative sleep parameters (e.g., sleep latency and sleep durations); and four items assessing regularity, quality,

and depth of sleep on a 0-3 scale were 0 = *excellent* and 3 = *poor*. Insomnia severity is indicated by the sum of the item scores. Scores range from 0-60 whereby 20 is a useful cut-off for clinical insomnia, and the RCI value was calculated as 6 (based on information in Sateia & Buysse, 2010). The PIRS-20 is found to respond greatly to clinical change and has a test-retest reliability of 0.92 and Cronbach's alpha of 0.95 (Sateia & Buysse, 2010).

#### *The Expanded Consensus Sleep Diary for Morning (CSD-M)*

Sleep diaries are the gold-standard for assessment of sleep continuity variables in both research and clinical practice. The CSD-M (Carney et al., 2012) is a self-report measure developed by a group of experts in order to obtain a standardized measure of sleep. It is an expanded version of the Consensus Sleep Diary including 10 items that report on the previous night's sleep (e.g., time in bed, sleep duration, sleep awakenings, and quality of sleep), items reporting on alcohol, caffeine and sleep medication intake, and space for additional comments (Carney et al., 2012). This sleep diary is to be completed daily, preferably one hour after waking, and has a third-grade reading level (Carney et al., 2012). In terms of validity, there is very limited research comparing the validation of the CSD-M with objective sleep measures, however Levinson and colleagues (Levenson et al., 2015) found that compared with actigraphy (an objective sleep measure), a sleep diary was more accurate at identifying older adults with insomnia.

### **2.2.3 Secondary outcome measures**

#### *Depression, Anxiety, and Stress Scale (DASS-21)*

The DASS-21 is a shorter version of the DASS-42 which measures the negative emotional states of depression, anxiety, and stress through a 42 item self-report questionnaire (Lovibond & Lovibond, 1995). Each of the three DASS-21 scales contains 7 items. These items are rated on a 4-point Likert scale that assesses the severity/frequency to which individuals have experienced each symptom over the last week ranging from *did not apply to me at all* (0) to *applied to me very much, or most of the time* (3). The RCI values were calculated as 3.7 for



depression, 3.5 for anxiety, and 3.4 for stress, with clinical cut-off scores of 7, 6, and 9 respectively (based on data in Henry & Crawford, 2005). Internal consistency demonstrated by the DASS-21 is high with Cronbach's alpha's of 0.88-0.94 for depression, 0.82-0.87 for anxiety, and 0.90-0.91 for stress (Antony, Bieling, Cox, Enns, & Swinson, 1998). Strong reliability and consistency of the DASS-21 has been shown in both clinical and non-clinical samples (Antony et al., 1998; J. D. Henry & Crawford, 2005). Moreover, correlations are high between the three scales, typically being greater than .60 (Lovibond & Lovibond, 1995), as well as high correlations with other validation measures including the Beck Depression Inventory –II (.76), Beck Anxiety Inventory (.74), and Positive and Negative Affect Schedule-NA (.74) (Gloster et al., 2008).

#### *The Maslach Burnout Inventory Educators Survey (MBI-ES)*

The MBI-ES (Maslach, Jackson, & Leiter, 1996) is an adaptation of the MBI whereby the word *recipient* is replaced by *student*. This was completed at the beginning of baseline and end of intervention to measure the two core burnout dimensions of *emotional exhaustion* and *depersonalization (cynicism)*. The emotional exhaustion subscale consists of nine items (e.g., “I feel emotionally drained from my work”) and the cynicism subscale consists of five items (e.g., “I feel I treat some students as if they were impersonal objects”). Items are rated on a scale of 1 to 7, where individuals rate how often they experience feelings associated with each item where 1 = *never* and 7 = *daily*. The RCI values were calculated as 9 for emotional exhaustion and 7 for depersonalization, with clinical cut-off scores of 26 and 13 respectively. Internal consistency of the *emotional exhaustion* subscale has been shown to range from  $\alpha = 0.88-.90$  and internal consistency of the *depersonalization* subscale ranges from  $\alpha = .74-.86$  (Whitehead, Ryba, & O'Driscoll, 2000).

### **2.3 Design and Procedure**

To carry out this research, a multiple-baseline design across participants with placebo control was used (Kazdin, 2010). This design allowed us to obtain baseline assessment of sleep

and wellbeing over a one-week period, as well as assessment of sleep and wellbeing over a 5 to 14 day placebo period and a staggered entry into the active intervention phase. By repeating the measures twice in baseline the baseline phase allowed for assessment of the baseline stability of the measures. This phase also allowed us to establish the existing pattern of sleep and wellbeing in participants. Placebo phases allowed for the determination of any expectancy effects as a result of taking pills, as well as blinding of both participants and the researcher. This then reduces bias arising from knowledge of treatment assignments. Staggered entry into the active intervention phase allowed for any replication of changes from baseline to be identified when treatment began, demonstrating experimental control (Kazdin, 2010).

Teachers meeting the study criteria were invited by email to make an appointment at the University of Canterbury or a place of convenience for them such as their school or home to discuss the study and participation. During the initial appointment, the teacher was provided with a detailed information sheet and consent form (see Appendix D), and information about the study including its aims, the requirements of participants, and any known risks, and were advised that participants agreeing to take part in the study would receive a placebo pill for a short length of time which would be unknown to both the participant and researcher. All teachers were provided with adequate opportunity to ask any questions, and were also informed that they could withdraw from the study without penalty at any time. All teachers who attended an initial appointment agreed to continue, and written informed consent was obtained from each.

As mentioned above, the study followed a multiple-baseline-across-participants design with placebo and was split into four phases: a baseline phase, a placebo phase, the micronutrient phase and a follow-up phase. Once eligibility and informed consent was established, all participants were randomized into one of three sequences determining baseline, placebo and the micronutrient formula treatment phases. Randomisation was completed by a research student not involved in the study whereby 17 numbers were generated (a mix of ones, twos and threes representing each baseline) using <http://www.randomization.com>, a website which uses a

random number generator to randomise participants into blocks of 3. One generated list was blindly selected and pills were packed according to the randomisation code by a pharmacist. Thus both participants and researcher were blind as to what sequence participants were allocated until after the study's completion. Participants were then followed up three months after completion of the study. The baseline, placebo and micronutrient intervention phases are described below.

### **2.3.1 Baseline phase**

Once eligibility and informed consent were established, the researcher met participants prior to the start of baseline to go over the questionnaires and answer any questions. Participants were assigned an identification number, given in order from 1 through 17, representing which (blinded) sequence they had been assigned to. At this appointment participants received the CSD-M sleep diary which was used daily throughout baseline to record their sleep. Sufficient pills for 4 weeks (combining placebo and micronutrients in numbers determined by the allocated sequence), were provided in sachet format and, given to participants with instructions as to what date to start taking them, and to make sure they take the pills with plenty of food and water.

All participants started the one-week baseline phase on the same day, and completed the PIRS-20, DASS-21 and MBI-ES measures online using Qualtrics. Sleep was recorded daily using the CSD-M. Participants were contacted via phone at the end of the one-week baseline to see how the first week was going and to answer any questions. At the end of the baseline phase, participants again completed the PIRS-20 and DASS-21 online.

### **2.3.2 Intervention phase**

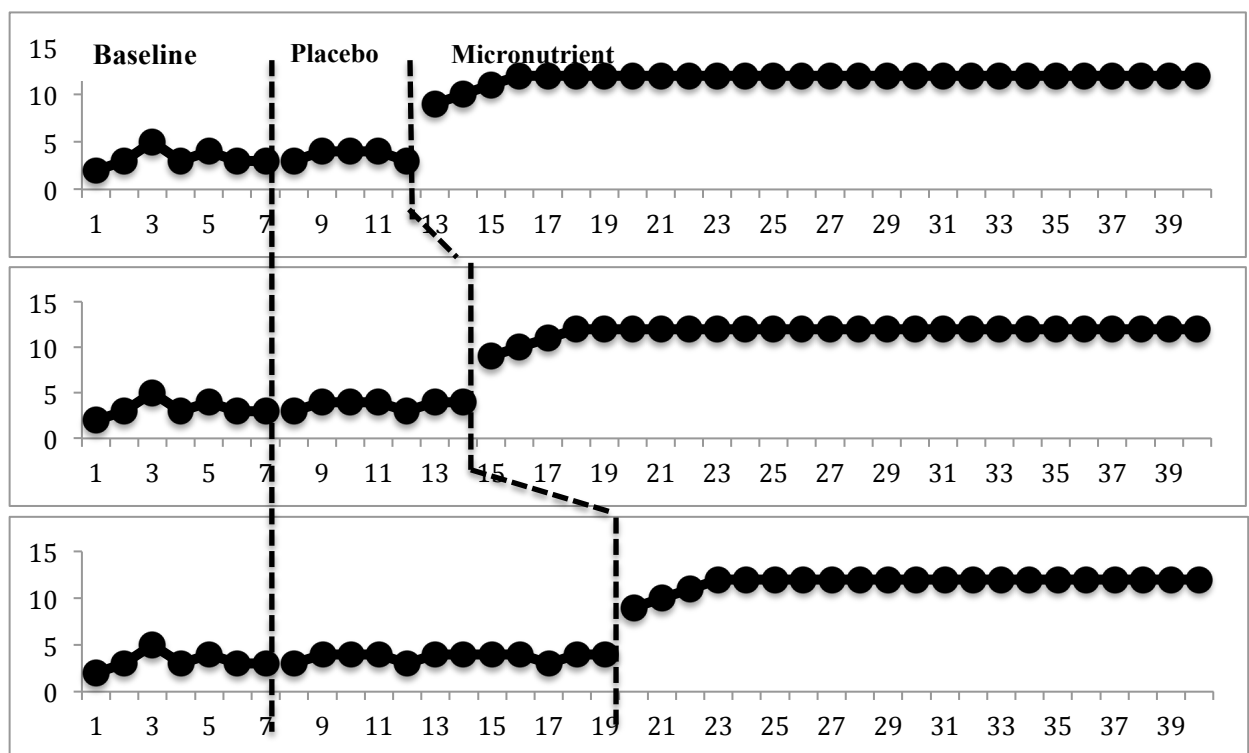
#### *Intervention, titration and dosage*

The micronutrient formula used was EMPowerplus Advanced (EMP+) developed by Truehope ([www.truehope.com](http://www.truehope.com)) and is a broad-spectrum micronutrient formula containing 14 vitamins, 16 trace minerals, 3 amino acids and 3 antioxidants (see Appendix A). Micronutrient pill dose was titrated up over four days to eight capsules per day, in two doses of four capsules

morning and night, taken with plenty of food and water. Participants were provided with EMP+ at no cost for the duration of the study. The placebo product, also provided by Truehope, contained fiber acacia gum, maltodextrin, cocoa powder and riboflavin powder and was visually identical to the active product. It was emphasized to participants the importance of taking the pills with plenty of food and water to minimize the likelihood of any side effects.

Participants transitioned from the baseline phase into the intervention phase at the beginning of term 4 of the school year, where they received both placebo and micronutrients. These sequences varied, with each group receiving a placebo for differing phase lengths, as follows (also see Figure 2 below):

1. Five days placebo phase then switch to a ten-week active intervention phase.
2. Nine days placebo phase then switch to an eight week and 5 days active intervention phase.
3. Fourteen days placebo phase then switch to an eight-week active intervention phase.



*Figure 2.* Gives an example of the multiple-baseline design with the baseline, placebo and micronutrient phases. As shown, placebo lengths differ for each of the three baselines (e.g., 5,9, or 14 days), and micronutrient phases ranged from 8-10 weeks.

In these phases, participants transitioned from placebo to micronutrients without their knowledge (or the knowledge of the researcher). As described above, the pharmacist constructed the required sequences of pills according to the randomization schedule, as this ensured both the researcher and participants would be blinded. Participants received the first four weeks of pills in a sachet format (see Figure 3 below) meaning each four pill dose sets were placed in separate envelopes to give 28 days supply in all. These sachets were dispensed in a continuous roll and were labelled with the participant identification number, labelled morning or tea dose, and what day to be taken. This allowed participants to tear off each envelope when needed and allowed for each participant to transition from the placebo to micronutrients at the correct time without their knowledge. Participants were advised that the pills would be in sachet format for the first four weeks in order for participants to get used to taking the pills daily. For the remainder of the intervention the pills came in bottle format (see Figure 4 below), whereby participants took 4 pills out of the bottle themselves twice a day. Therefore, the placebo phase for each group varied and all participants received micronutrients for a minimum of 8 weeks and maximum of 10 weeks. Participants were instructed to contact the researcher if they experienced any adverse effects from taking the pills.

During the intervention phase, participants completed the PIRS-20 and DASS-21 online at days five, nine and 14 and then the end of at weeks 4 and 10. Participants also completed the MBI-ES online at the end of week 10. A side effect questionnaire was also completed at these time points (see Appendix E), which asked about side effects including stomach aches, nausea and headaches. Any issues while taking the pills were addressed and side effects monitored and remedied via lowering the dosage. Participants met with the researcher monthly in order to check how they felt the study was going and if there were any changes they had noticed. These appointments were also important to check for side effects, compliance and any problems with participation. Participants were provided with more pills as needed at these appointments and any unused pills were returned. All participants received a \$25 supermarket voucher at

completion of the study as a koha (gift) and thank-you for taking part. Participants were also provided with contact details of the EMP+ supplier so that they could purchase the micronutrients themselves should they wish to do so.

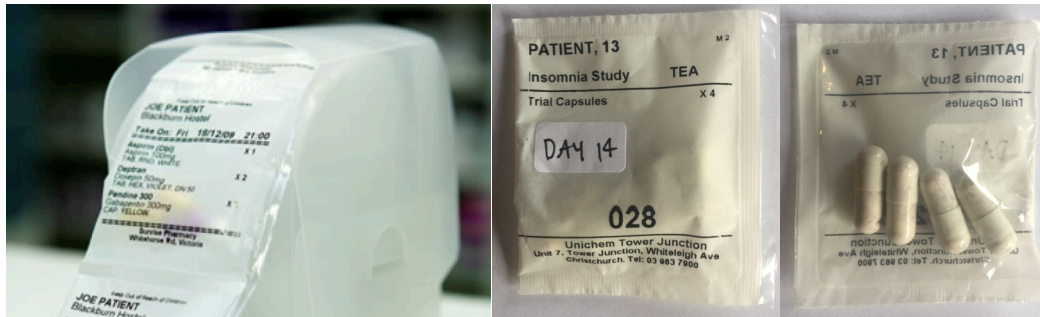


Figure 3. Shows the sachet packaging used to supply the pills.



Figure 4. Shows the bottle format used to supply the pills.

### 2.3.3 Three month follow-up

All participants were contacted and asked to complete an online follow-up questionnaire three months after the end of their treatment phase. This questionnaire contained the PIRS-20 and DASS-21 measures referring to the previous week, questions regarding whether or not participants decided to continue taking the micronutrients, as well as a 5-point Likert scale asking participants to rate their experience in the study, using ratings from *poor* (0) to *excellent* (5).

### 2.4 Data Analyses

The primary outcome measures of this research included the CSD-M daily diary data and PIRS-20. Regarding the CSD-M, standard multiple-baseline time series graphs were used to detect individual changes across CSD-M variables of sleep onset latency, number of night

wakings, sleep efficiency, total time asleep, and subjective sleep quality from baseline to intervention. The Percentage Exceeding the Median (PEM) (Ma, 2006) was used as the single-case effect size for this research. The PEM is the “percentage of Phase B data points exceeding the median of the baseline phase” (Ma, 2006; in the current study "exceeding" should be taken as in the clinical direction, which is reduction for variables such as frequency of night wakings and increase for variables such as sleep efficiency). To calculate PEM a horizontal line is drawn from the baseline phase through the treatment phase indicating the baseline median and the number of data points falling above or below the median in the direction of clinical change is counted in the treatment phase and expressed as a percent of the total data points in that phase (Ma, 2009). PEM interpretation is given by the criterion of Scruggs and colleagues (Scruggs, Mastropieri, Cook, & Escobar, 1986) whereby  $70\% < \text{PEM} < 90\%$  = a moderate ES and  $\text{PEM} > 90\%$  = a large ES (after Lothian et al., 2016).

Individual changes in the PIRS-20 primary outcome measure and DASS-21 and MBI-ES secondary outcome measures over baseline and intervention phases were analysed using modified Brinley plots (Blampied, 2017; Jacobson & Truax, 1991). Modified Brinley plots provide a visual analysis of individual change over time so that intervention effects can be recognised, whilst also placing each individual participant's scores in the context of those of all other participants. Each individual's data at time 1 - baseline (x-axis) and time 2 – posttreatment (Y axis) are displayed on a scatter plot as a coordinate pair. Intervention effects are evident when scores/data points deviate from the diagonal line of no change. If data points do not deviate from the line of no change, the baseline score = intervention score meaning no treatment effect has occurred. When clinical change is indicated by a reduction in scores, data points situated above the diagonal line signify greater impairment and data points situated below the diagonal line signify less impairment (or improvement), and when a high score indicates better functioning, the opposite holds true. Additional lines may be supplied to signify clinical cut-off scores, which enables clinical significance of outcomes to be easily seen. Clinical cut-offs can be employed for

any dependant variable and can assist in interpretation of therapeutic change through classifying individuals in terms of clinical status and symptoms levels (Blampied, 2017). Arrows are displayed on the graph in order to aid interpretation through displaying the direction of desired change. Therefore, if reduction of initial score at baseline indicates clinical improvement the arrow will point downwards, and if increase of the initial score at baseline indicates clinical improvement the arrow will point upwards. In terms of this research, scores falling below the horizontal clinical cut-off line indicate a non-clinical score at time-point two. When looking at the graph it is important to note the transition of individuals from the clinical to the nonclinical section of the graph (Gordon, Rucklidge, Blampied, & Johnstone, 2015). Therefore, in terms of this research a treatment effect will be evident if scores deviate below the line of no change for the PIRS-20, DASS-21 and MBI-ES. Textual information on the graph can also provide Effect Size information, such as Cohen's  $d$  (Blampied, 2017).

Change from baseline to intervention can be classified using the Reliable Change Index (Jacobson & Truax, 1991). The  $SE_M$  for each measure is used to calculate the RCI, which signifies the amount of change needed for a score to lie outside the expected range due to measurement error alone (Jacobson & Truax, 1991). Thus, the RCI indicates *how* much change has occurred over treatment, and someone who has crossed the cut-off point will have changed considerably. The RCI was set at a value such that individuals whose change scores exceed this value can be noted as displaying reliable change ( $p < .05$ ). The Effect Size (ES) for PIRS-20, DASS-21 and MBI-ES outcomes was calculated two ways, first, using the Common Language Effect Size (CLES; Lakens, 2013), which gives the likelihood (expressed as a percentage) that after controlling for individual differences any participant will have an improved score at the second measurement, and, second, the standardized mean difference effect size, Cohen's  $d_{av}$ , calculated using software provided by Cumming (2012), where  $d_{av}$  is the ES for the within-subjects design. The ES confidence interval, also calculated using software provided by Cumming (2012), was set at 95% and signifies that if the trial was repeated numerous times, we



can expect the true value of the ES to fall in this range 95% of the time. Therefore, if the CI does not cross zero we can conclude that there has been a reliable treatment effect, as the ES is reliably not zero, and that the mean at time two is statistically significantly different to the mean at time one (Cumming, 2012).

### 3. Results

The following sections present the results of the intervention as assessed by the primary and secondary outcome measures. Individual changes across CSD-M variables over experimental phases were analysed using conventional time series graphs and visual analysis and are presented first. Individual changes in the PIRS-20 primary measure and DASS-21 and MBI-ES secondary measures over experimental phases were analysed using modified Brinley plots (Blampied, 2017; Jacobson & Truax, 1991) and are presented second. Demographic characteristics of the final sample are presented in Table 2 below.

Figure 1 shows the flow of participants through the trial. Of the 17 participating teachers, 11 taught at primary schools and 6 taught at secondary schools. One participant indicated they had a past anxiety disorder that was no longer current and no participants disclosed that they had a current psychiatric disorder.

Table 2: *Demographic Characteristics of Final Sample*

Characteristic	Final Sample
Sex, n (%)	
Male	5 (30)
Female	12 (70)
Age in years, mean (SD)	48.1 (10.1)
Household Income, n (%)	
From \$40,000 to \$60,000	1 (6)
From \$60,000 to \$80,000	5 (29)
More than \$80,000	11 (65)
Education, n (%)	
Post-secondary (e.g., diploma)	1 (6)
University Degree	11 (65)
Other	5 (29)
Ethnic origin, n (%)	
New Zealand European/Pakeha	17 (100)

In terms of gender distribution, the participants were a fair representation of the New Zealand teaching population as a whole, as the latest teaching census reports 73% of NZ teachers are female and 27% male (Ministry of Education, 2005), but the sample had an overrepresentation of NZ European/Pakeha in comparison to the census which reports 79% of NZ teachers nationwide identify as European/Pakeha, 10% identify as Maori, 2% as Pasifika and 2% as Asian (Ministry of Education, 2004).

### 3.1 Safety, Adherence and Participant Experience

Reported side effects experienced by participants were of mild to moderate intensity (see Tables 3 and 4; one participant experienced moderate intensity headaches, as indicated in Table 4). Side effects were remedied through instructions to take the pills with more food and water (see Table 3). During the placebo phase, headaches were reported by four participants and gastrointestinal disturbances by two participants. These side effects were reported to only last 2-3 days during this time. In the micronutrient phase, headaches were reported in nine (53%) participants as an adverse event; however, for the majority of participants these were mild and transitory, with one participant experiencing moderate intensity headaches. Gastrointestinal disturbance was reported by three participants; however, these were reported by each of these participants at one visit and were gone by the next. Agitation and dry mouth were reported by eight and six participants respectively; however, they were unclear as to whether this was due to the micronutrients. All side effects were predominantly reported at the beginning of the micronutrient phase and lessened over the course of the intervention. Additionally, one participant experienced gastrointestinal symptoms and fatigue toward the end of the intervention. To remedy this, the dosage was lowered to four pills per day with the participant reporting that the symptoms had then decreased; however, at the end of the intervention the researcher was notified that these symptoms were not a result of the intervention but of an undiagnosed infection.

Table 3. *Treatment-emergent side effects reported by participants during the trial.*

<i>Adverse Event</i>	<i>Definitely Related</i>		<i>Possibly Related</i>	
	n	%	n	%
<b>Micronutrient Phase</b>				
Headache	1	6	8	47
Gastrointestinal Disturbance			3	18
Nausea			5	29
Dry Mouth			8	47
Agitation			6	35
Constipation			4	24
Abdominal Pain			4	24
<b>Placebo Phase</b>				
Headache			4	24
Gastrointestinal Disturbance			2	12

Table 4. *Treatment-emergent side effects reported by each individual participant during the trial.*

Participant	Micronutrient Phase							Placebo Phase	
	Headaches	Gastrointestinal Disturbance	Nausea	Dry Mouth	Agitation	Constipation	Abdominal Pain	Headaches	Gastrointestinal Disturbance
1									
2									
3	✓	✓	✓	✓	✓	✓	✓		
4			✓	✓			✓		
5									
6	✓			✓	✓		✓		✓
7								✓	✓
8				✓				✓	
9	✓ (Moderate)	✓	✓		✓		✓		
10									
11	✓			✓	✓	✓		✓	
12	✓		✓		✓			✓	
13	✓			✓		✓			
14	✓	✓	✓	✓	✓	✓			
15	✓			✓					
16									
17									

Note: ✓ indicates participants experiencing mild and transitory side effects unless otherwise stated.

Overall, adherence to the intervention protocol was good and 16 out of 17 participants (94%) achieved compliance of greater than 80% and therefore did not miss a significant number of doses. Of the compliant participants, one participant took the micronutrients at a lower dose of four pills per day for the last three weeks of the intervention as a response to perceived side effects (see above). For the one non-compliant participant (P13 - who achieved a compliance rate of 77%) non-compliance was largely due to forgetting to take the scheduled doses.

### 3.2 Sleep Diary Data: Time Series Data Analyses

At the end of the intervention phase, all 17 participants had supplied complete data sets for the CSD-M. The diary data for each participant for each night are presented visually below in the form of separate multiple-baseline time series graphs for each CSD-M variable. Transitions between trial phases are indicated by vertical lines and phase labels. Percentage Exceeding the Median (PEM) was used as a summary of the effects experienced by each participant and were averaged across participants for each DV to assess the overall outcomes of the intervention (Tables 5 and 6). As previously stated in the Methods section, in the current study "exceeding" should be taken as in the clinical direction (i.e., the number of data points falling above or below

the median in the direction of clinical change is counted in the treatment phase and expressed as a percent). Based on the PEM, of the 17 participants, sleep diary data show that 14 (82%) reported one or more beneficial effects of the micronutrient intervention with moderate to large effect sizes (as shown by the PEM, defined in the Method section above). Of these 14 participants, all demonstrated moderate to large effects for sleep efficiency, 10 for Total Sleep Time (TST), 8 for reduced night wakings, 3 for subjective sleep quality and two for sleep onset latency (SOL). Further, of these 14 participants, 12 (85.7%) indicated multiple improvements. At follow up, these 14 participants rated their experience participating in the study as a mean of 4.21 (SD = 1.12) on a 5-point Likert scale ranging from poor (0) to excellent (5). The remaining three participants, P13, P14, P15, reported no moderate or large effects. Of these three, participant P13 was the one non-compliant participant, and participant P14 reported multiple side effects (however, these were only “possibly related” to intervention). These participants rated their experience in the study as 3, 4 and 4 respectively. Only the mean PEM for sleep efficiency demonstrated a moderately large treatment effect overall, with TST approaching moderate effect overall (Table 5). In contrast, during the placebo phase mean no PEM for any of the sleep variables achieved even a moderate overall effect size, with sleep efficiency reaching the maximum of 61% (Table 6). The results are discussed in detail in the following sections.

Table 5. *Percentage Exceeding the Median in the Micronutrient Phase for each Participant and each Dependant Variable from the Consensus Sleep Diary-Morning.*

Participant	Sleep latency	Night wake frequency	Sleep efficiency	Total sleep time	Subjective quality	Mean PEM	95% CI (±)
1*	N/A	52	<b>90</b>	<b>77</b>	45	66.00	10.02
2*	N/A	52	<b>70</b>	<b>78</b>	46	61.50	7.13
3	N/A	34	<b>91</b>	55	23	50.75	14.23
4*	6	61	<b>75</b>	<b>86</b>	9	57.75	17.83
5*	<b>93</b>	<b>99</b>	<b>93</b>	<b>91</b>	0	75.20	20.03
6*	N/A	49	<b>81</b>	<b>71</b>	12	53.25	14.53
7*	63	<b>79</b>	<b>92</b>	<b>85</b>	65	76.80	5.98
8*	<b>98</b>	<b>77</b>	<b>93</b>	<b>97</b>	<b>81</b>	89.20	4.56
9*	N/A	<b>100</b>	<b>75</b>	45	58	69.50	11.29
10*	N/A	<b>91</b>	<b>92</b>	51	<b>100</b>	83.50	10.48
11*	38	<b>75</b>	<b>86</b>	56	8	56.25	14.71
12*	N/A	69	<b>90</b>	<b>77</b>	54	72.50	7.16
13	N/A	20	63	32	6	30.25	11.54
14	N/A	53	57	46	32	47.00	5.22
15	N/A	17	17	37	17	22.00	4.75
16*	N/A	<b>87</b>	<b>87</b>	<b>85</b>	<b>98</b>	89.25	2.81
17*	N/A	<b>71</b>	<b>80</b>	<b>82</b>	33	66.50	10.86
Mean	59.60	63.88	78.35	67.71	40.41		
95% CI (±)	18.32	11.92	9.15	9.66	15.17		

Note: Bold numbers indicate a moderate to large effect size (>70%). Mean = mean percentage; CI = Confidence Interval; N/A = not applicable; \* = participants experiencing more than one positive effect.

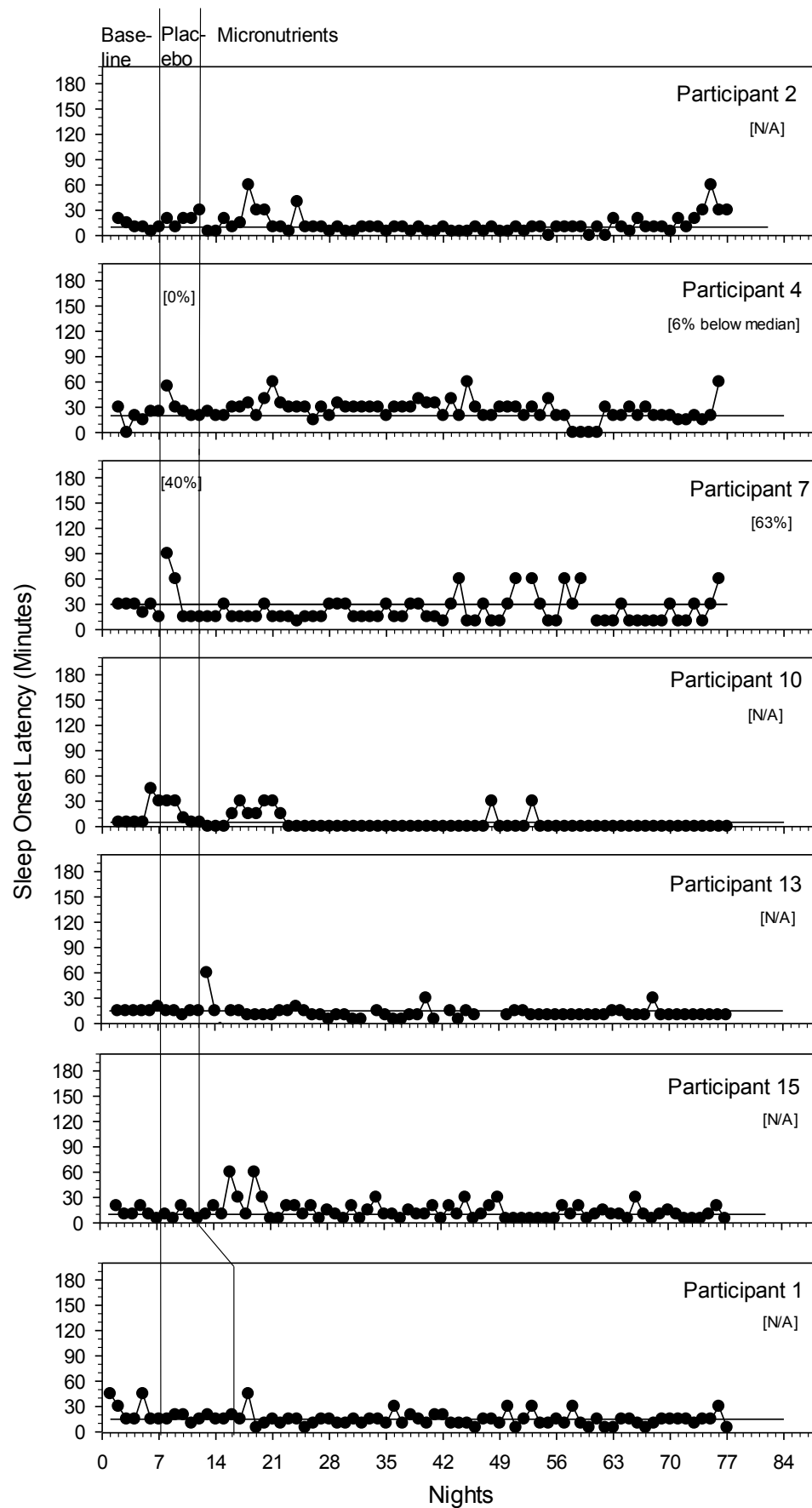
Table 6. *Percentage Exceeding the Median in the Placebo Phase for each Participant and each Dependant Variable from the Consensus Sleep Diary-Morning.*

Participant	Sleep latency	Night wake frequency	Sleep efficiency	Total sleep time	Subjective quality	Mean PEM	95% CI (±)
1	N/A	22	43	57	44	41.50	6.88
2	N/A	40	20	60	20	35.00	9.10
3	N/A	0	<b>71</b>	64	33	42.00	15.45
4	0	20	60	60	0	35.00	14.26
5	<b>86</b>	<b>71</b>	57	50	0	52.80	14.70
6	N/A	33	<b>100</b>	56	22	52.75	16.42
7	40	20	<b>80</b>	<b>80</b>	20	50.00	16.47
8	<b>86</b>	57	<b>86</b>	<b>86</b>	<b>86</b>	80.20	6.89
9	N/A	67	<b>89</b>	44	56	64.00	9.09
10	N/A	<b>100</b>	<b>100</b>	60	<b>100</b>	90.00	9.51
11	0	<b>89</b>	34	33	0	31.20	17.53
12	N/A	57	64	<b>86</b>	29	59.00	11.18
13	N/A	0	20	0	0	5.00	4.75
14	N/A	<b>100</b>	67	44	56	66.75	11.44
15	N/A	20	20	20	0	15.00	4.75
16	N/A	<b>71</b>	<b>71</b>	<b>78</b>	<b>93</b>	78.25	4.93
17	N/A	<b>93</b>	57	14	14	44.50	18.14
Mean	42.40	50.59	61.12	52.47	33.71		
95% CI (±)	20.45	16.17	12.57	11.77	16.10		

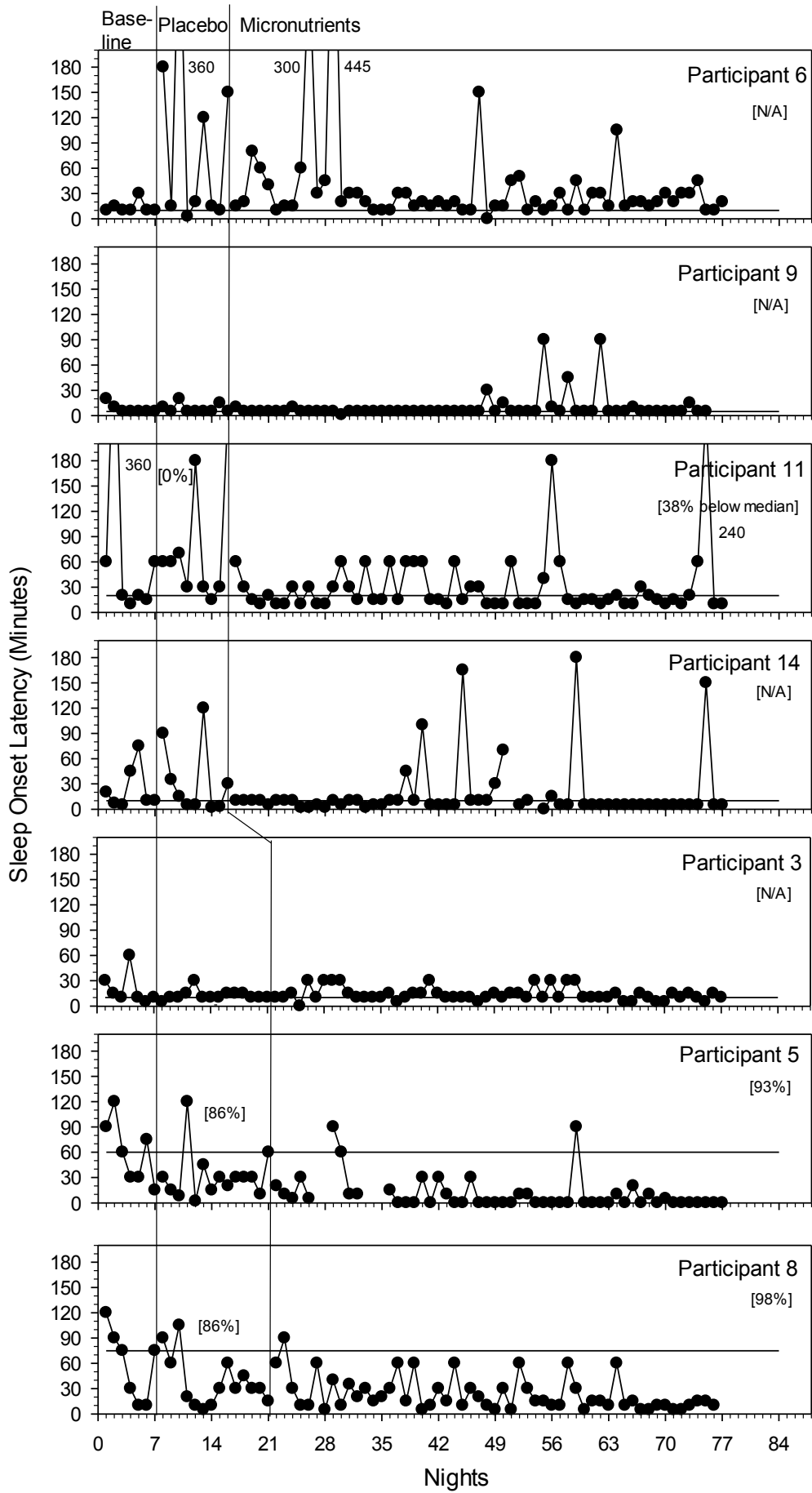
Note: Bold numbers indicate a moderate to large effect size (>70%). Mean = mean percentage; CI = Confidence Interval; N/A = not applicable

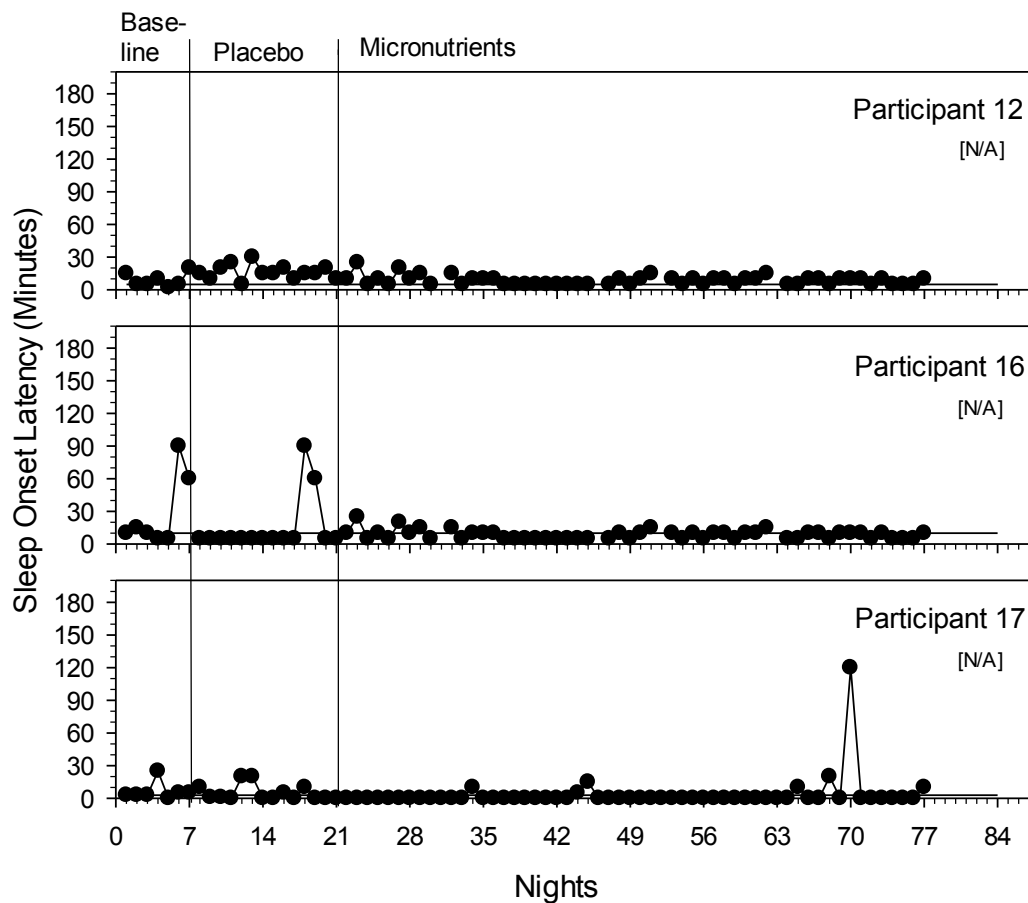
### 3.2.1 Sleep onset latency

Sleep onset latency (SOL) refers to how long it takes an individual to transition from full wakefulness to sleep. SOL may be problematic for individuals when it is consistently longer than desired and/or when it is highly variable, so that on a substantial number of (unpredictable) nights the individual has difficulty falling asleep. Both aspects of SOL are examined below. By convention, if it takes an individual longer than 30 minutes to make this transition, then they are classified as having an excessive SOL and only 6/17 participants experienced consistent problems with SOL in baseline. Time-series data for all participants on this measure are presented below in Figure 5. Participants P5 and P8 both showed large improvements in SOL throughout the micronutrient phase in comparison to baseline and placebo phases, as can be seen by decreases in latency values and the variability of data. Although SOL reduction can be seen in the placebo phase, participant P7 displays further SOL reduction as the micronutrient phase continues, with only slight variability in weeks five and six. Participants P11 and P14 both show increased variability in SOL throughout baseline and placebo phases, but both SOL and variability reduce during the micronutrient phase for P11; and P14 shows an immediate positive effect at the beginning of the micronutrient phase, which continues throughout, except for some nights with higher variability during week three. Although participant P6 does not display a SOL problem during baseline, SOL was problematic in the placebo phase, and a positive effect is seen in the micronutrient phase through the reduction in outliers and variability. The remaining 11 participants did not show any treatment effect on this measure, as they did not have a problem with SOL to begin with.









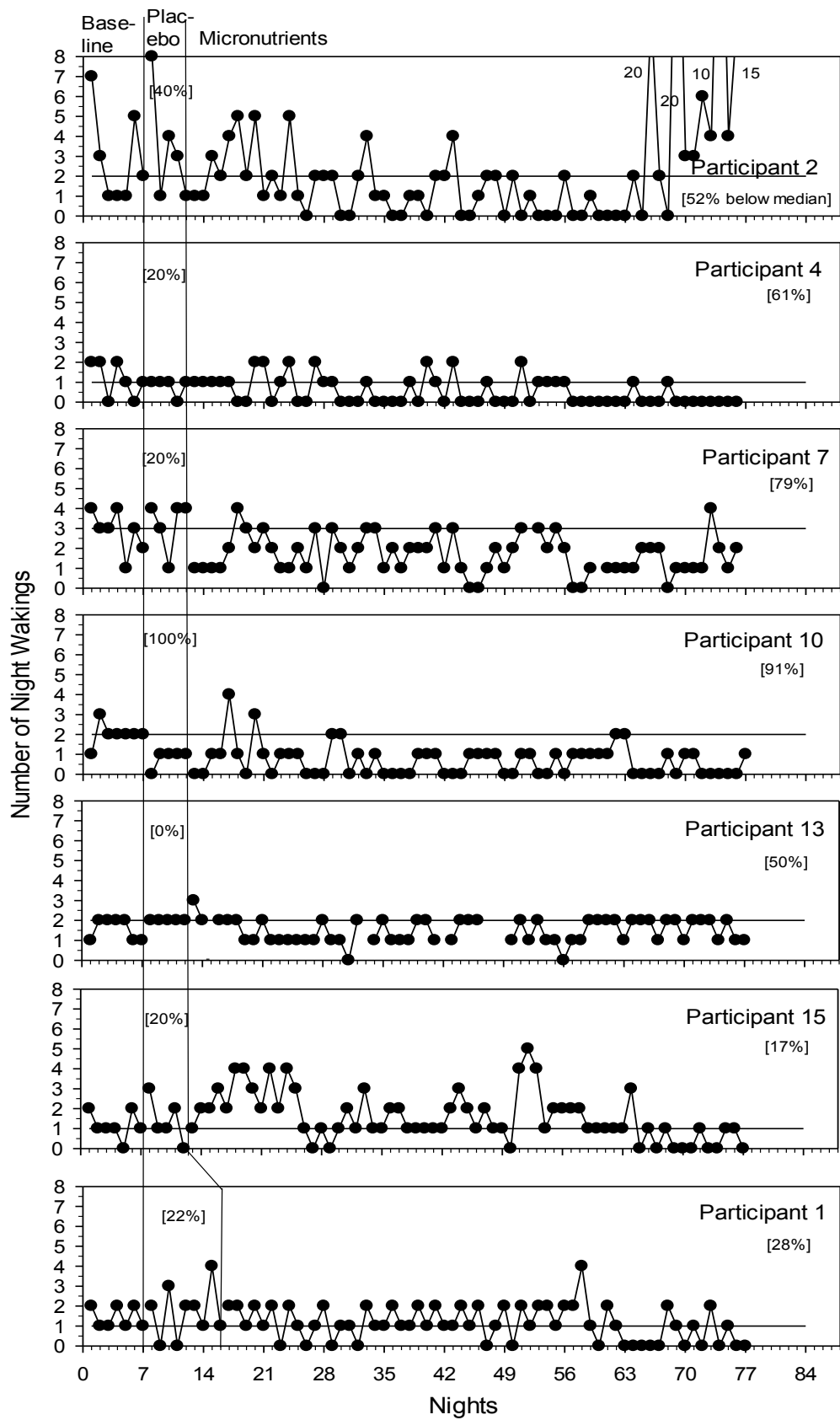
*Figure 5.* Times series graphs of sleep diary self-reported nightly sleep onset latency (SOL; in minutes) for each participant. The first vertical line shows the transition from baseline to placebo phase at one week and the second vertical line shows the transition from placebo to micronutrient intervention condition at 5, 9, or 14 days. The horizontal line shows the baseline median and the percentage reports the percentage exceeding the median (PEM) single-case effect size for each participant if applicable. As explained in the Methods section, PEM goes in the clinical direction. Numbers on the graphs indicate the value of data points that are off-scale.

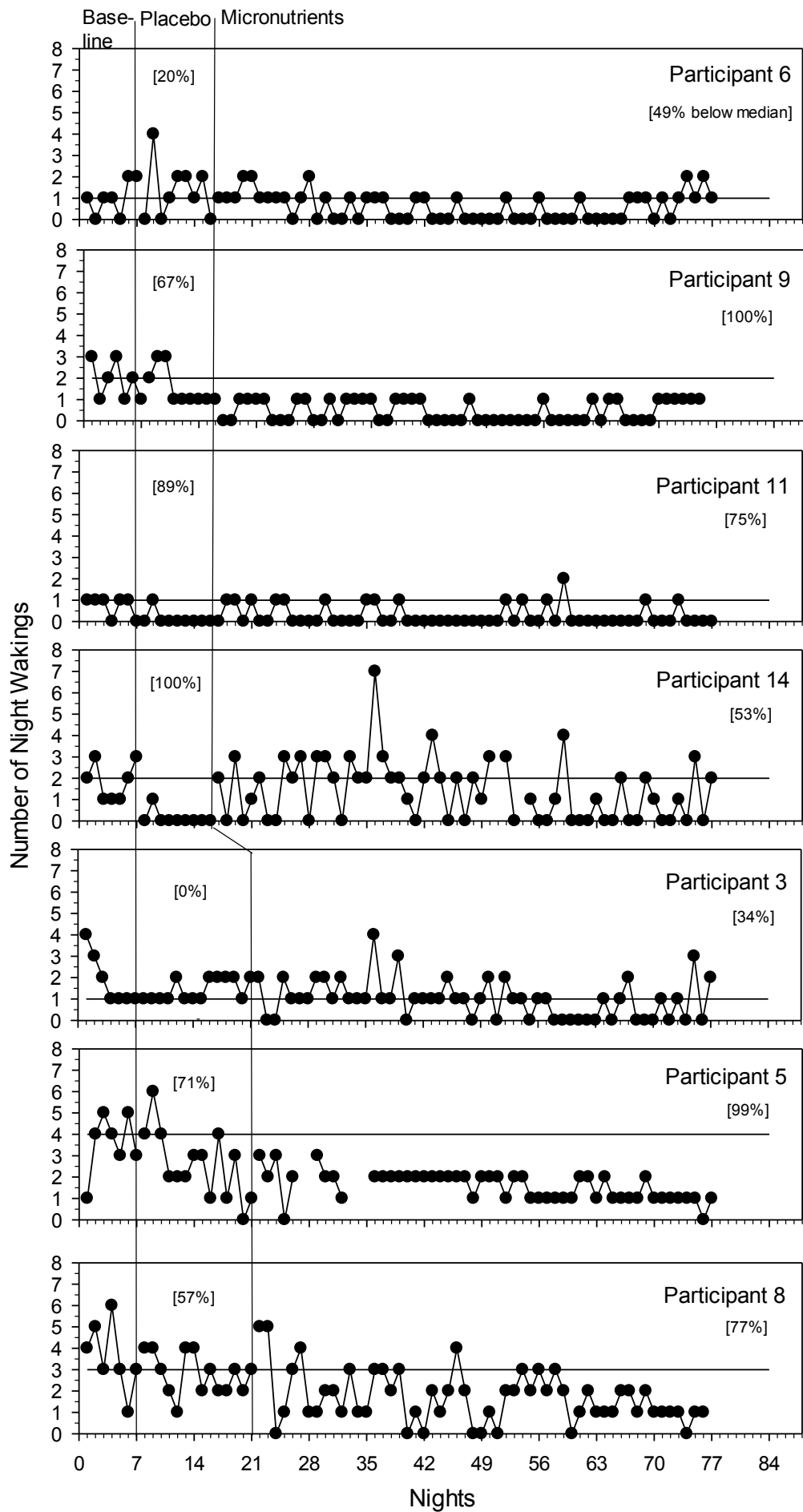
### 3.2.2 Night wake frequency

Frequency of night waking refers to how many times participants awoke during each night over the course of the trial, with frequent night waking on at least three out of seven nights being part of the definition of insomnia. As for SOL, variability of night-waking from night to night may be problematic for individuals even if on occasion they have nights with few or no wakings. Time-series data for all participants on this measure are presented below in Figure 6. The solid horizontal line represents the median. All participants reported awaking during the night at least once during the baseline phase. Participants P7, P10, P9, P11, P5, P8, P16 and P17 all display moderate to large effect sizes for this measure as shown in Table 5. Of these

participants, P10, P9, P11, P8, P16 and P17 show a decrease in night waking during the placebo phase, with P8 and P17 displaying high variability. Participants P7, P10 and P17 show an immediate decrease in wakings in the first four days of the micronutrient phase, variability and wakings then increase, before both gradually decrease as the intervention continues. P16 displays decreased wakings with some variability in the first and last week of the micronutrient phase. Participants P9, P11, P5 and P8 also display a gradual positive effect in the level and trend of data via a gradual decrease in number of wakings and variability throughout the intervention phase. It is important to note that participants P10, P11 and P17 experienced a greater reduction in wakings in the placebo phase compared to the micronutrient phase; however, the remaining five participants experienced a greater reduction in wakings during the micronutrient phase as shown by the PEM.

Of those who did not show a moderate to large effect on this measure, small treatment effects are displayed by participants P2, P4, P13, P14, and P12. Participant P2 displays high variability throughout the trial; however, this reduces toward the end of intervention and a positive effect in the level and trend of data is seen (increase at end reportedly due to a storm with strong winds and shared accommodation). Participant P4 began to show a decrease in night wakings from day five of the micronutrient phase and by week seven variability and wakings decreased substantially. Participant P14 displays an initial placebo response during the placebo phase. Wakings then increase and become variable throughout the first five weeks of the intervention, with both then reducing in the last three weeks of the intervention. Although variability in wakings remained throughout the trial for participants P12 and P13, a positive trend throughout the micronutrient phase is still shown. Participant P14 experienced greater reduction in wakings in the placebo phase; however, the remaining four participants experienced a greater reduction in wakings during the micronutrient phase. Of the remaining participants, participants P15, P1, P6 and P3 showed no beneficial effect of the intervention on night wake frequency.





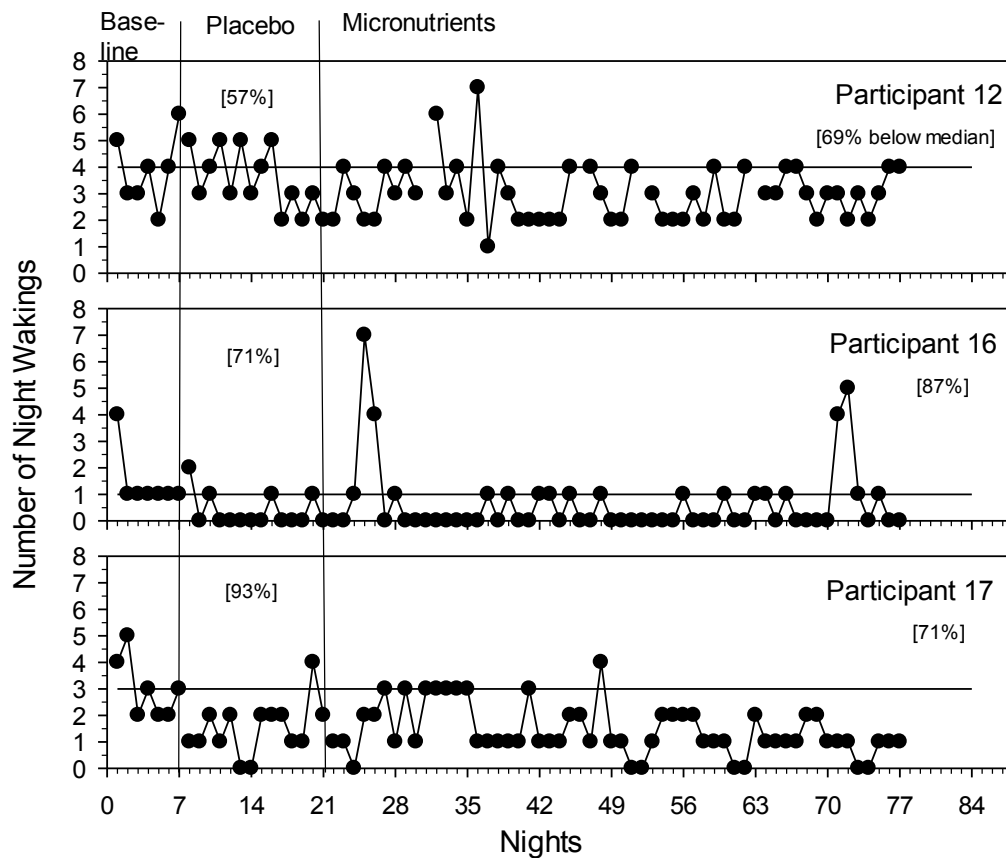


Figure 6. Times series graphs of sleep diary self-reported nightly waking frequency. Numbers on the graphs indicate the value of data points that are off-scale. Phase and median lines and percentages are as for Figure 5.

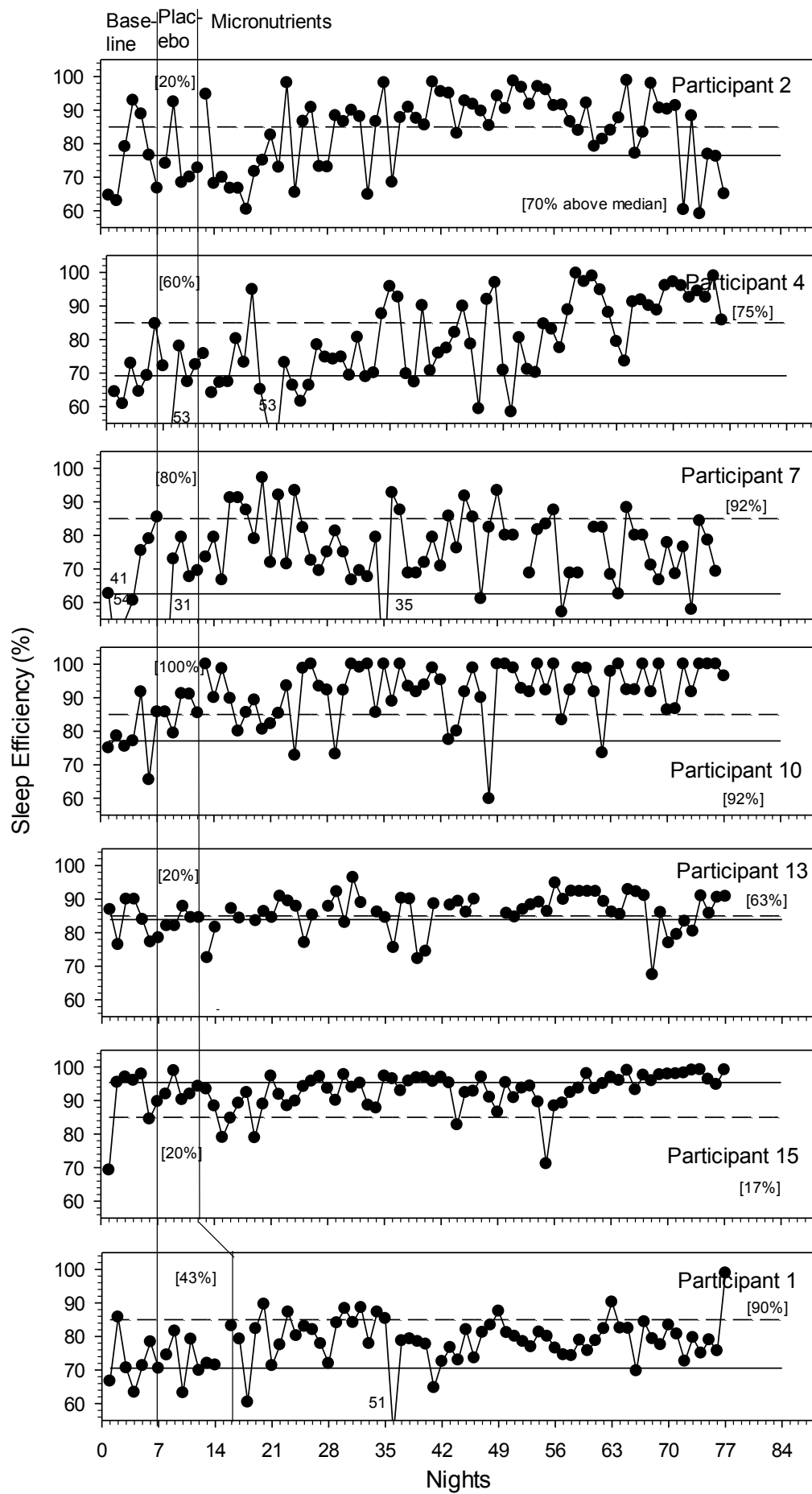
### 3.2.3 Sleep efficiency

Sleep efficiency is a measure that combines multiple elements of sleep latency and total time asleep and expresses the sum as a proportion of total time spent in bed. Time-series data for all participants displaying low SE% in baseline are presented below in Figure 7. Individuals who obtain a SE% of less than 85% are considered to be poor sleepers (Spielman, Saskin, & Thorpy, 1987). This threshold is represented in Figure 7 as a dashed horizontal line. The solid horizontal line represents the median (from which the PEM is calculated). At baseline, two participants (P13 and P15) were at or above the SE% threshold; and levels of SE% were maintained during intervention for participants P15 and increased slightly for P13.

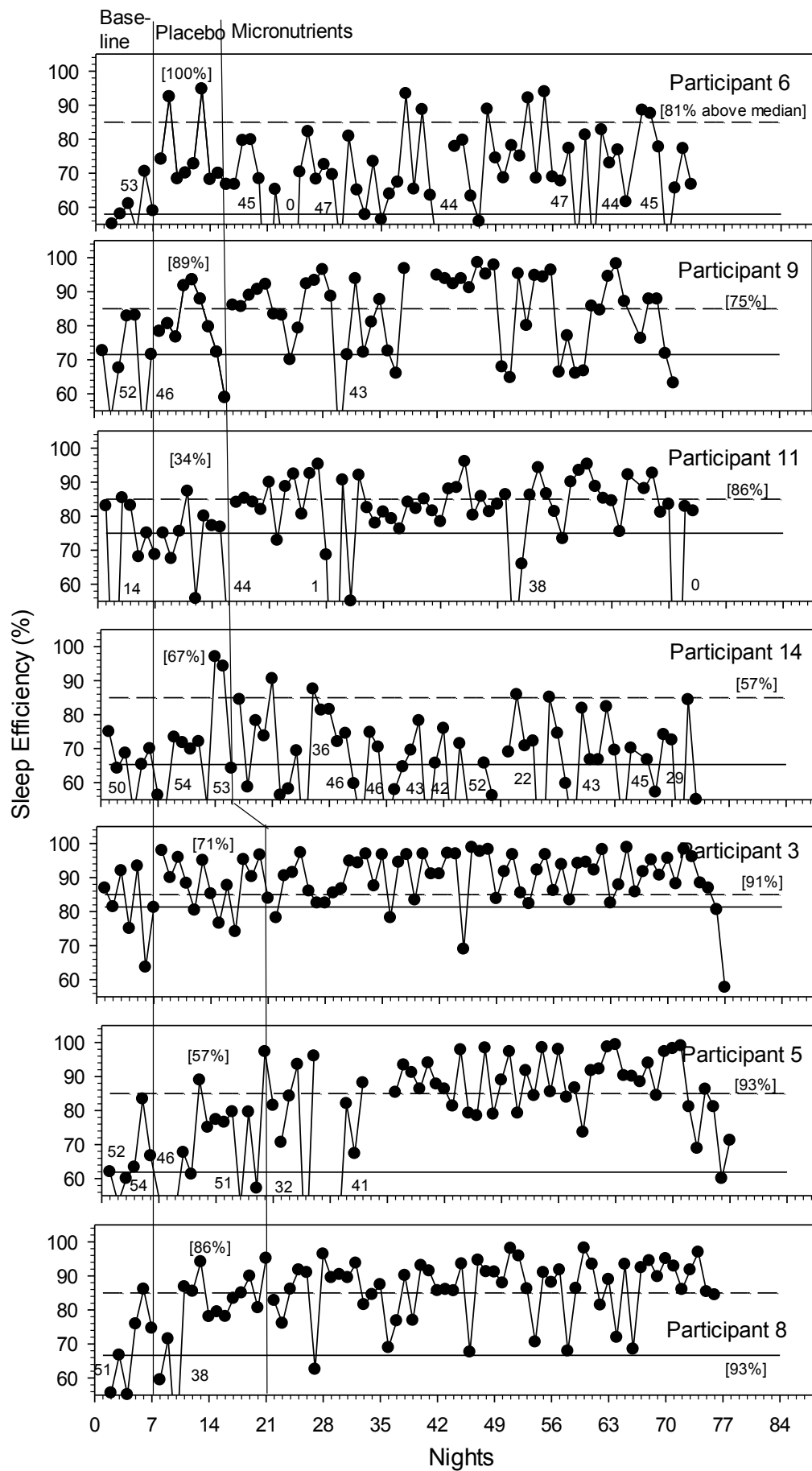
Of 17 participants, 14 showed moderate to large improvements in SE%. Of these, participants P2, P4, and P7 show continual gradual improvement of sleep efficiency throughout

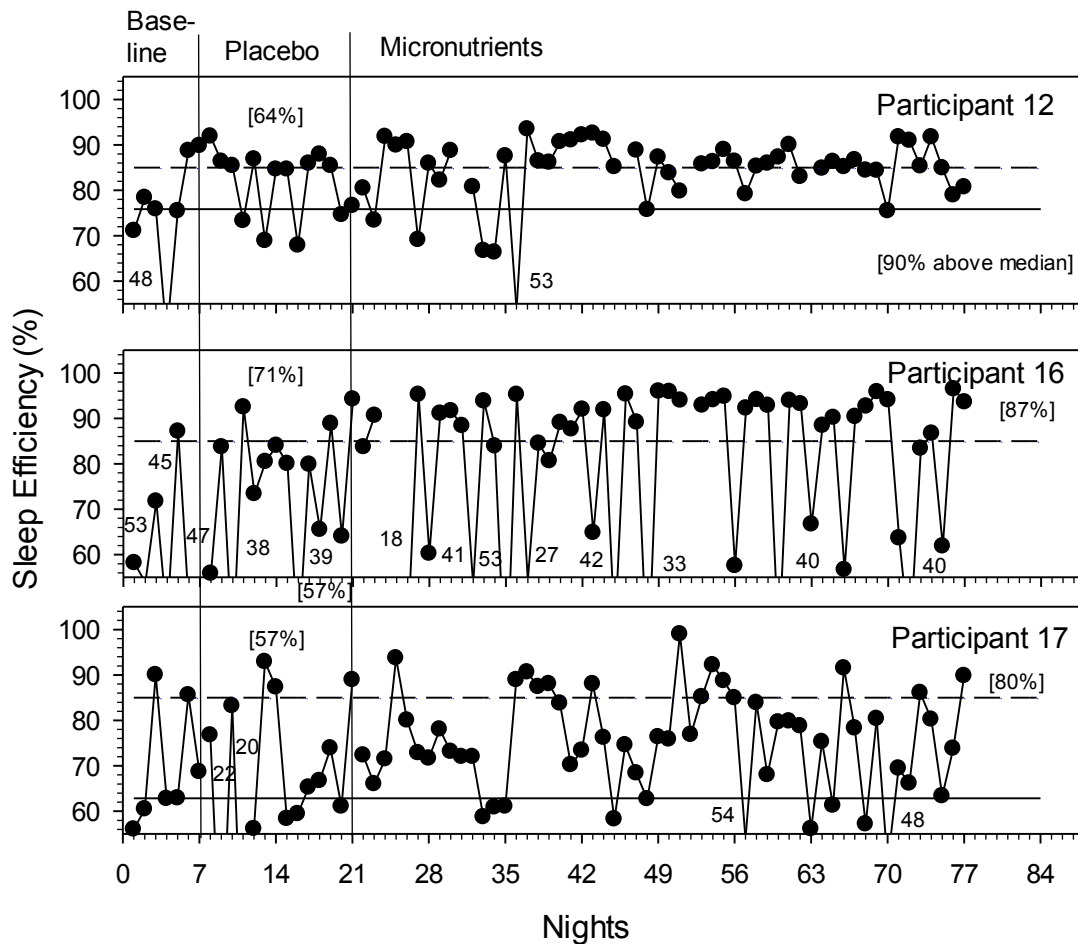
the micronutrient phase, despite high variability throughout. Participants P1 and P5 also show gradual improvement at the beginning of the micronutrient phase, SE% then increases and unlike the participants above, P1 and P5's SE% variability reduces (P5's variability increases at the end due to being out of routine with social events). In contrast, participants P10 and P11 show a more immediate positive effect on SE% at the beginning of the micronutrient phase, which persists throughout the remainder of the trial for both participants despite some variability. For participants P8 and P16 a slight positive trend can be seen during the placebo phase as compared to the baseline phase, and a gradual increased positive effect is seen in the micronutrient phase. In terms of variability of SE%, participant P8's SE% remains relatively stable, with the odd night of low SE%. On the other hand participant P16 continues to display high variability despite overall improved SE%. Participants P6 and P9 also display low SE% in baseline and an increase in placebo. As both participants enter the micronutrient phase, variability remains high throughout the trial, however an increase in SE% compared to baseline can still be seen as the trial continues. For participant P12, a delayed positive effect is displayed from week three of the micronutrient phase and remains throughout. Participant P17 also displays a positive effect in the micronutrient phase in comparison to baseline and placebo; however, variability continues to remain high. Of the 14 participants showing moderate to large effect sizes, participant P3 was the only individual to display relatively high SE% during baseline. SE% increased and remained high for the remainder of the intervention. Participants P2, P6 and P9 experienced greater SE% in the placebo phase; however, the remaining 11 participants experienced a greater SE% during the micronutrient phase.

Of the three participants (P13, P14 and P15) who did not display a large to moderate effect size on SE%, participant P14 displayed greater SE% in the placebo phase in comparison to the micronutrient phase.









*Figure 7.* Times series graphs of sleep diary self-reported sleep efficiency percentage (Total time asleep/Total time in bed x 100) for each participant. Numbers on the graphs indicate the value of data points that are off-scale. Phase lines and percentages are as for Figure 5. The dashed horizontal line represents the 85% sleep efficiency criterion, and the solid horizontal line represents the baseline median.

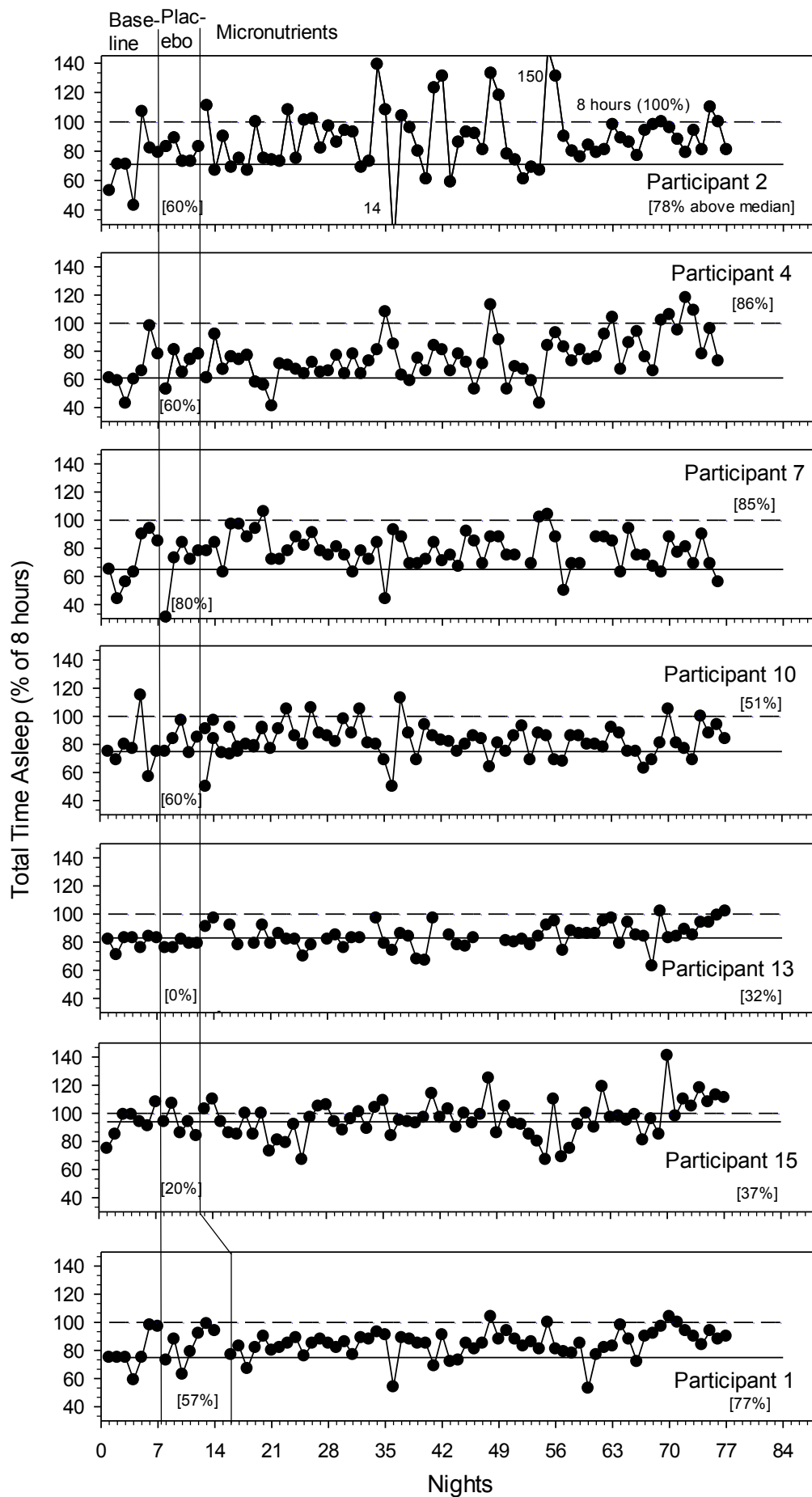
### 3.2.4 Total sleep time

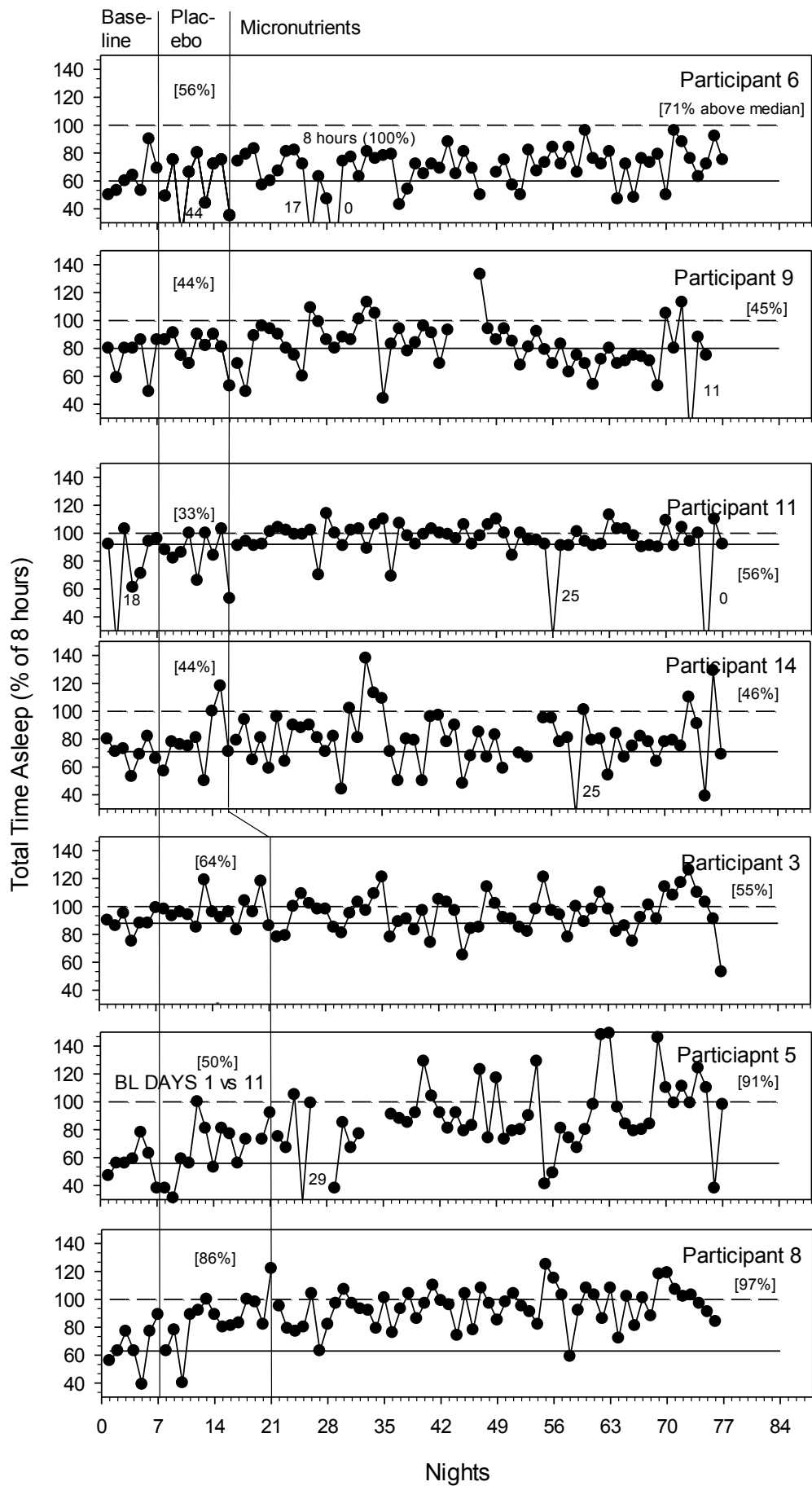
Total sleep time (TST) is defined as the duration of time participants spent asleep during each night, and is calculated as a percentage of eight hours (taken as a conventional length of good sleep for adults). Time-series data for all participants displaying problems in TST in baseline are presented below in Figure 8. Eight hours of sleep is represented as a dashed horizontal line in Figure 8, and the median is represented as a solid horizontal line.

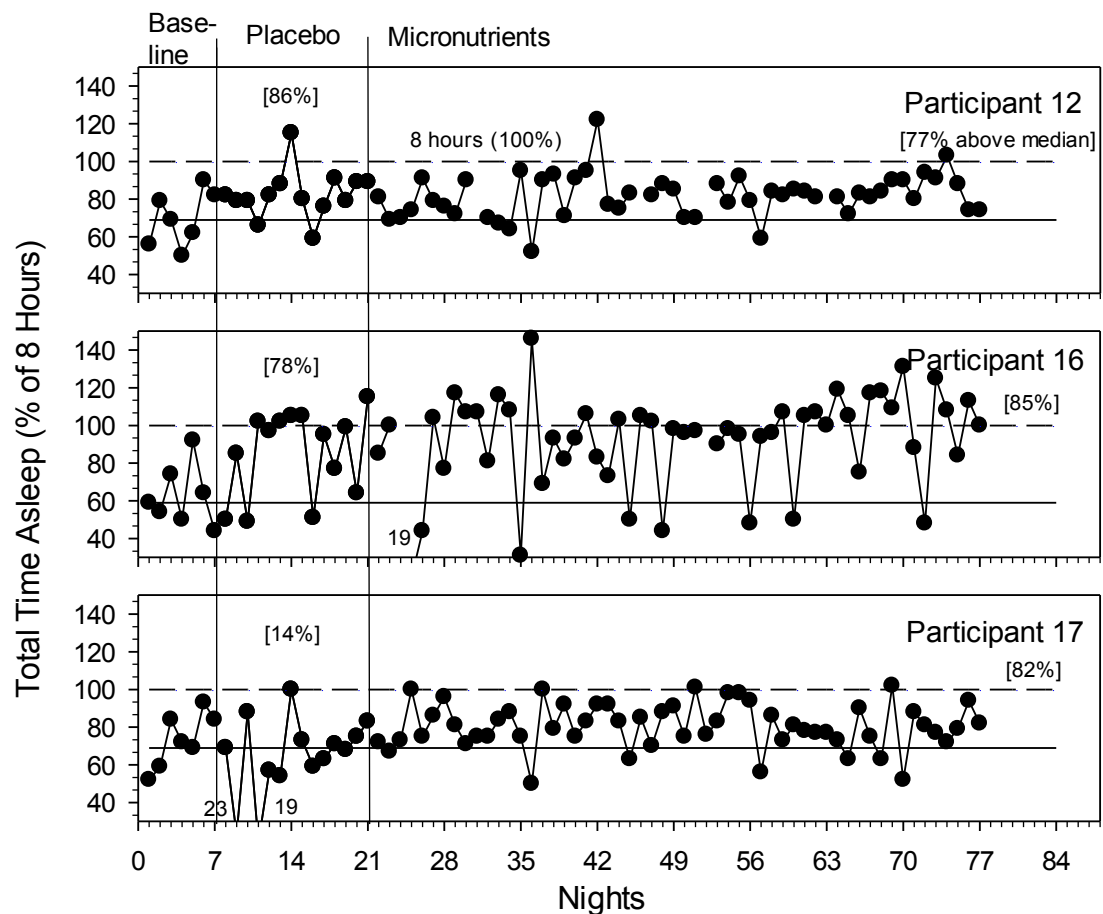
Of the participants who displayed a moderate to large improvement in TST, all displayed a gradual improvement as the micronutrient phase continues (i.e., there is no immediate change in the level and trend of TST observed). Participants P5 and P8 show the largest improvement in

TST over the micronutrient phase in comparison to baseline and placebo phases, and display steady positive trends. Additionally, participant P4 shows a positive delayed effect in TST from week six of the micronutrient phase. A similar trend is seen in participant P6 where improvement in TST is consistently shown from week five in the micronutrient phase, with the exception of three nights of lower TST. Participant P2 displays gradual improvement in TST in the micronutrient phase as compared to the baseline and placebo phases, with variability stabilizing in the last three weeks of the intervention. These participants display further improvement in the micronutrient phase compared to placebo. Participants P7, P1, P12 and P17 display moderate to large improvements in TST over the micronutrient phase. However, in comparison to the placebo phase this improvement is small for P7, and P12 shows greater improvement in the placebo phase.

Of those participants who did not show a substantial improvement in TST (P10, P13, P9, P11 and P14), participants P10, P13 and P11 maintained a stable TST percentage throughout the intervention, with slight improvements seen in the micronutrient phase in participants P13 and P11 relative to baseline and placebo. Participant P10 displayed greater increase in the placebo phase in comparison to the micronutrient phase. Participants P9, P14, and P3 displayed no beneficial change in TST after the micronutrient intervention.







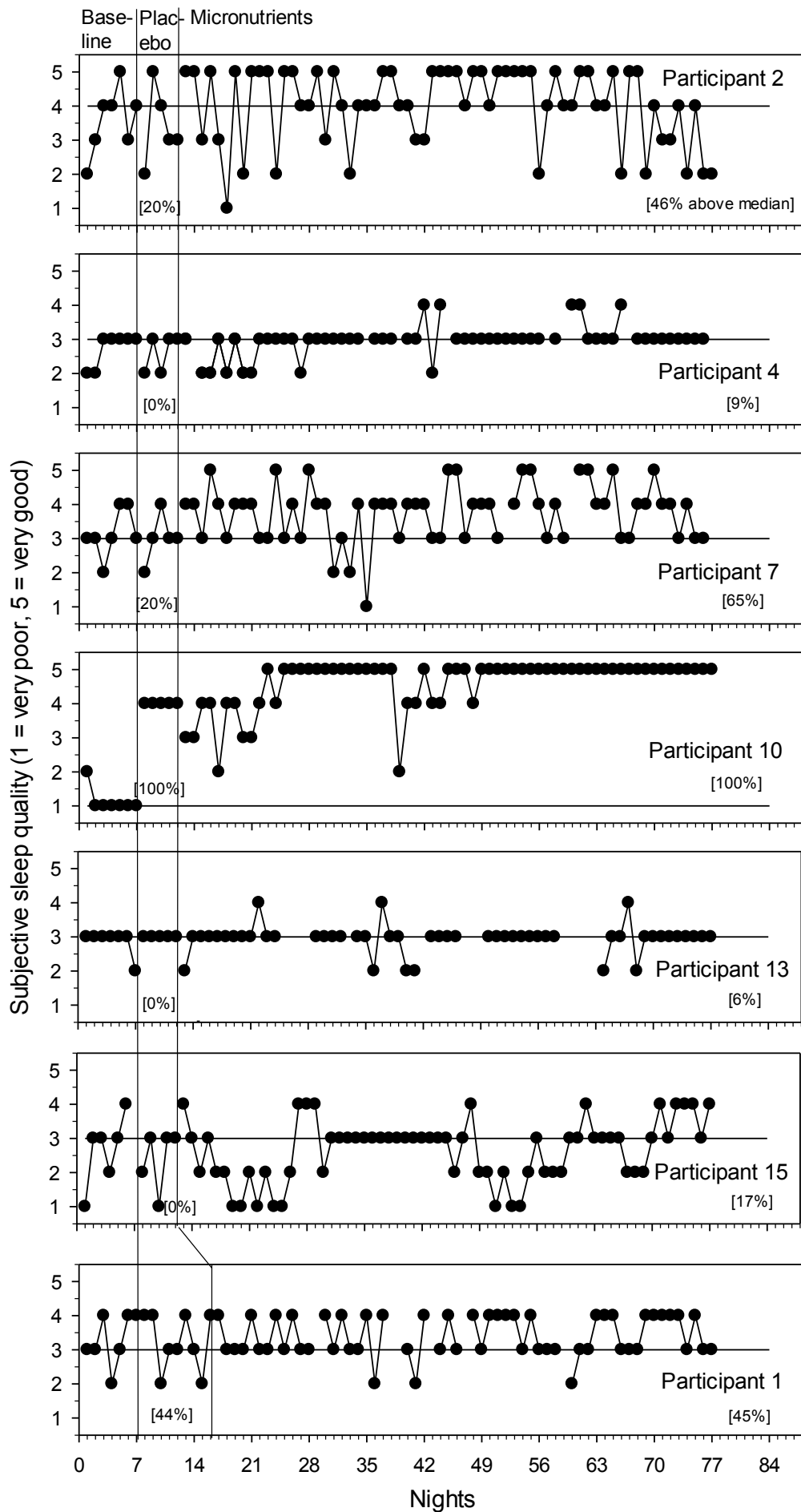
*Figure 8.* Times series graphs of sleep diary self-reported total nightly sleep duration expressed as a percentage of 8 hours (100% indicated by dashed horizontal line) for each participant. Numbers on the graphs indicate the value of data points that are off-scale. Phase and median lines and percentages are as for Figure 5.

### 3.2.5 Subjective sleep quality

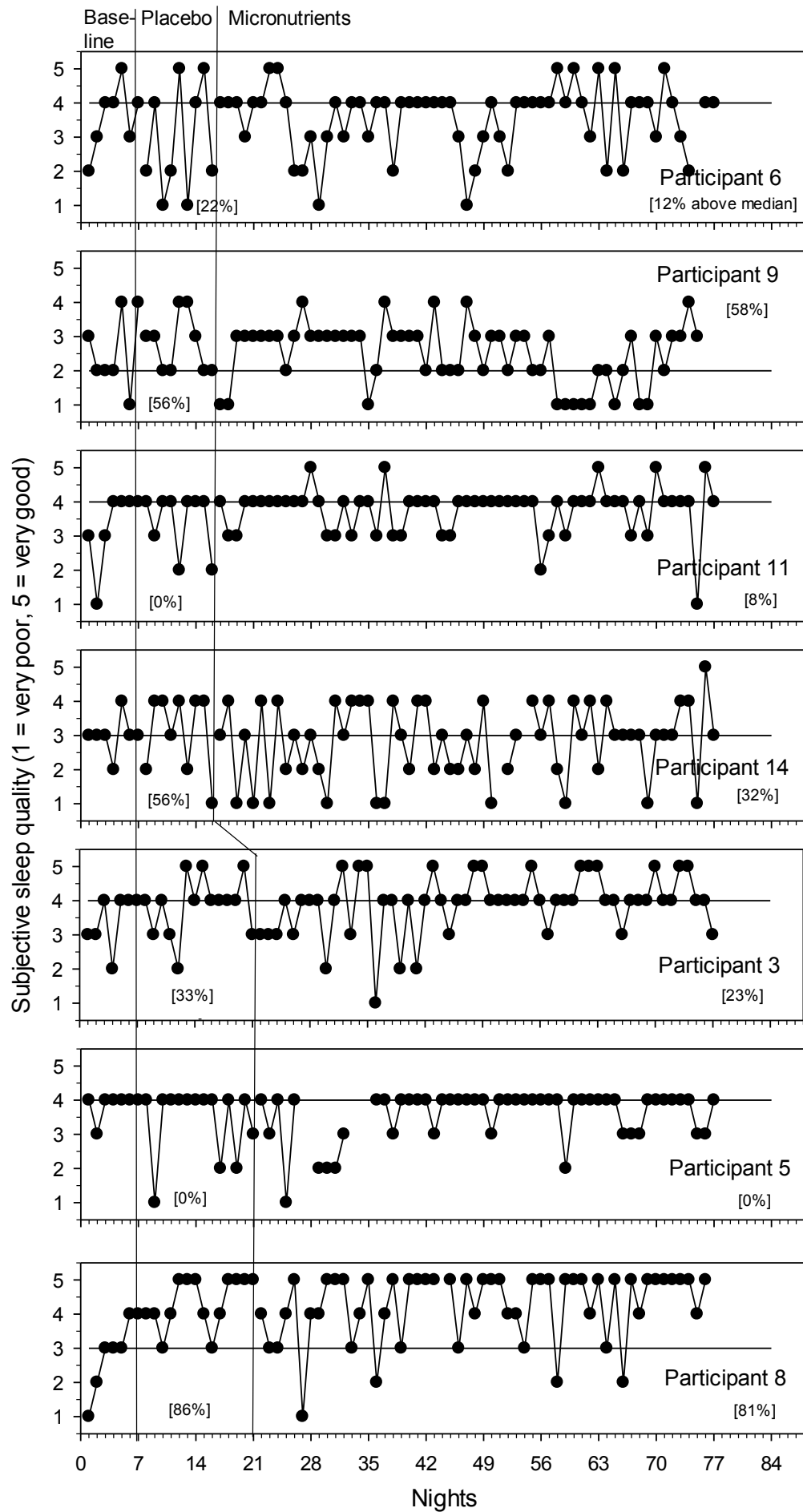
Subjective sleep quality refers to how participants rated the quality of their sleep throughout the trial on a scale of “very poor” to “very good”. Time-series data for participants displaying change on this measure are presented below in Figure 9. Only three participants (P8, P10 and P16) displayed moderate to large effect sizes in subjective ratings of their sleep quality. These three participants rated the quality of their sleep as “very poor” to “fair” during the baseline phase. In the placebo phase, ratings increase, however high variability is seen in participants P8 and P16. As participants enter the micronutrient phase, participant P10’s scores initially decrease after the placebo phase; however, subjective sleep quality is then generally rated as “very good” throughout the remainder of the trial, with slight variability during week

four as a result of an earthquake (large enough to produce sustained shaking over the city but without reported damage) and subsequent tsunami warnings during the night involving loud sirens. Furthermore, although participant P10 displays a placebo effect, a further increase in sleep quality ratings in the micronutrient phase is evident. Participant P8 displays a positive trend in comparison to baseline that steadily increases over the micronutrient phase with the average sleep quality rating noted as “very good”, and variability reduces at the end of the trial. Although participant P8 shows slightly higher ratings in the placebo phase, these ratings are maintained during the micronutrient phase. For participant P16, rated sleep quality initially decreases at the start of the micronutrient phase; however, a steady increase in sleep quality is seen over the remainder of the trial with average sleep quality rated as either “good” or “very good” (some variability is due to being woken up during the night by a young child). It is important to note however, that the increase from placebo to the micronutrient phase for P16 is small.

Of the participants who did not show substantive improvement, participants P7 and P12 showed a small treatment effect. For both participants, sleep quality ratings show no change throughout baseline and placebo phases. Participant P7’s ratings then increase during the micronutrient phase, and although sleep is variable, the majority of sleep quality ratings are either “good” or “very good” for remainder of the intervention. Participant P12 continues to display no change in sleep quality ratings until week three of the micronutrient phase, where sleep quality ratings increase, variability decreases and sleep quality ratings become more stable. Additionally, although effects are small, participants P2 and P17 show increased ratings during the micronutrient phase in comparison to baseline and placebo. Of the remaining participants, P4, P13, P15, P1, P6, P9, P11, P14, P3, and P5 showed no beneficial effect of micronutrients on subjective sleep quality from baseline to the end of intervention. This is largely due to the fact that all of these participants, except participant P9, were rating their sleep quality as either “fair” or “good” to begin with.







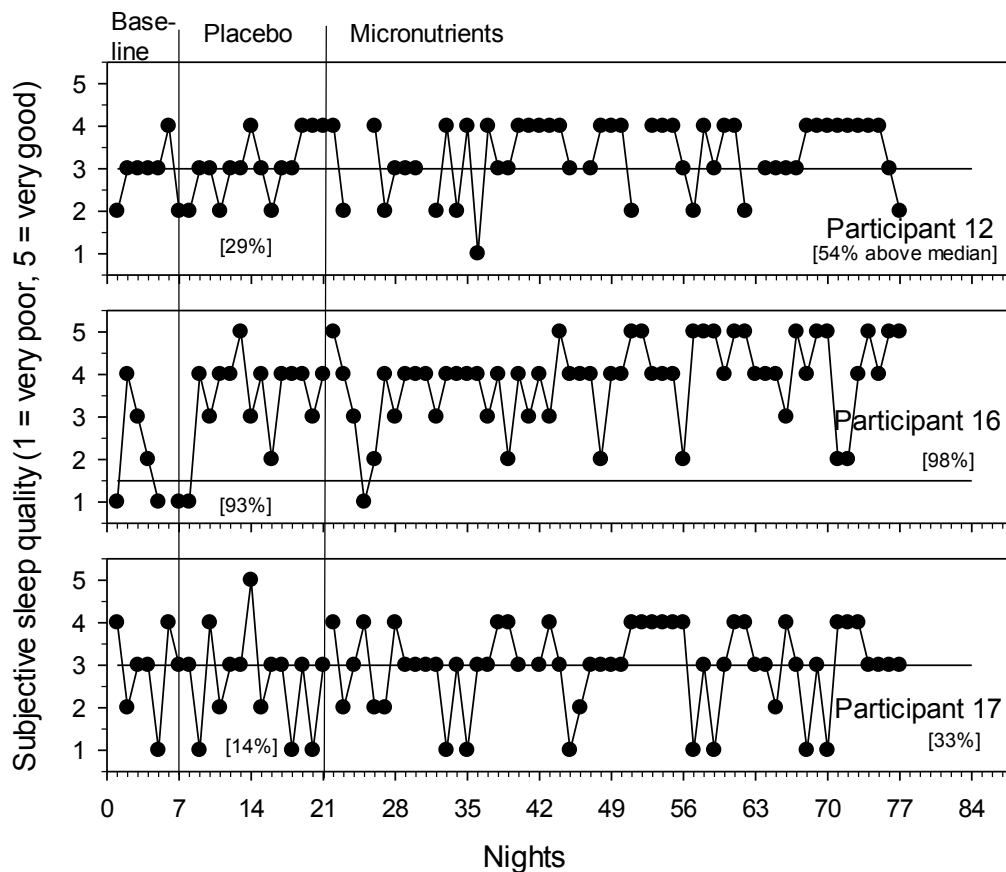


Figure 9. Times series graphs of sleep diary self-reported sleep quality ratings for each participant. Phase and median lines and percentages are as for Figure 5.

### 3.3 Modified Brinley Plot Analyses

Data for the PIRS-20, DASS-21 and MBI-ES are presented visually below as modified Brinley plots (see Figure 10 for the interpretation of these plots). For each measure, data are presented on these plots as the score for any individual at one time-point against the score of the same individual at a later time-point. As described earlier, scores that deviate from the diagonal line of no effect indicate a change from one time point to another, and thus any effect of an intervention if one has occurred during the time interval, with the extent of change being further quantified by reference to the Reliable Change Index (Weissman et al., 1997) and clinical cutoffs (based on prior research). For the PIRS-20, DASS-21 and MBI-ES, scores that deviate below the line of no change indicate a treatment effect, and therefore improvement. Refer to Figure 10 below for an interpretation of modified Brinley plots. Unless otherwise indicated, scores are referenced to the initial baseline score, thus showing change relative to initial baseline levels.

Additionally, to further aid in interpretation each figure below is accompanied with a Table displaying Cohen's  $d_{av}$ , the CLES, and the 95% confidence interval (CI) on  $d$  for each phase comparison. In the analysis of the data for the thesis, the modified Brinley plots were used to address three questions: (1) How stable was the measure during baseline? (2) What was the magnitude of the placebo effect, if any? and (3) was there an effect of the micronutrient treatment?

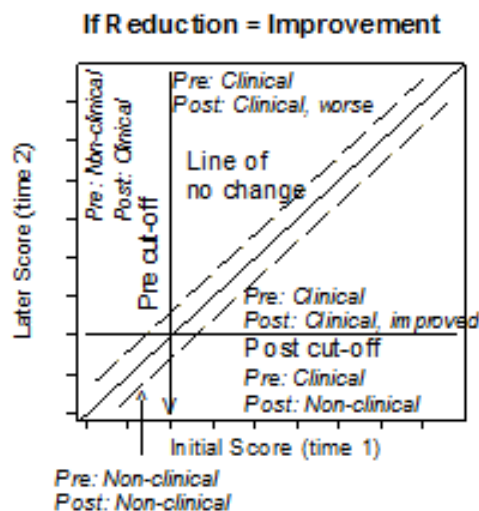


Figure 10. Modified Brinley plot interpretation of graph zones (after Blampied, 2017) when reduction in score indicates clinical improvement.

### 3.3.1 Primary measure

The following figures show the effect of the placebo and micronutrient intervention on insomnia as measured by the PIRS-20. Figure 11 (see below) assesses baseline stability of insomnia symptoms and tracks the placebo response for each of the three phase-length groups. For the relevant ES of Cohen's  $d_{av}$ , and CLES and the 95% CI on  $d$ , see Table 7 below. The initial plot presents baseline stability for phase-length group one (five days placebo), and shows three participants' scores exceed the lower RCI boundary, with two below the clinical cut-off. The CLES shows that the probability of participant's PIRS-20 scores being reduced at baseline two compared to initial baseline is 89%, and as the 95% CI on  $d$  does not cross zero, the mean level of change in scores is reliable after the one week baseline (i.e., the mean change in scores is significantly different from zero). Over the course of the next five days in the placebo phase, one

of these participants continued to reduce their PIRS-20 score relative to initial baseline, whilst the score for the other sits just below the clinical cut-off line. The remaining four participants display little mean change in PIRS-20 scores at placebo day five compared to initial baseline. The CLES shows that the probability of these participant's PIRS-20 scores being reduced (to any degree) in placebo compared to initial baseline is 95%. However, as the 95% CI on  $d$  crosses zero, the mean level of change in scores is not reliably different from zero.

The three plots in the middle of Figure 11 display change for phase-length group two (nine days placebo) across baseline and placebo phases. The initial plot presents baseline stability for group two, and shows that relative to their first baseline PIRS-20 score, participants demonstrate little mean level of change after the one-week baseline. Compared to their initial baseline score, three participants demonstrate a slight deterioration in PIRS-20 scores after one-week baseline, and are on the verge of demonstrating reliable deterioration as they sit on the upper RCI line. Over the course of the next two plots, participants show little mean level of change at placebo day five relative to initial baseline score, and by placebo day nine two participants reduced their scores below the clinical cut-off and demonstrate reliable positive change. The CLES shows that the probability of participant's PIRS-20 scores being reduced by placebo day nine compared to initial baseline is 90%. However, as 95% CI's on  $d$  for group two were not computable (because the data violated the requirements for iterative computation built into the software) it cannot be determined whether overall change is reliably different from zero.

The last four plots at the bottom of Figure 11 display change for phase duration group three. The initial plot presents baseline stability for group three (14 days placebo), and shows that relative to their first baseline PIRS-20 score, three participants show slight deterioration in scores after the one-week baseline, with one participant demonstrating reliable deterioration. However,  $d$  is not reliably different from zero. The remaining three participants display little change. The next plot demonstrates that group three displays an initial placebo effect, but over the course of the next two plots this effect stays fairly stable, indicating that over the whole

placebo phase there was no incremental increase in the placebo effect. By placebo day nine The CLES shows that the probability of participant's PIRS-20 scores being reduced in the placebo phase compared to initial baseline is 89%;  $d$  was not reliably different from zero.

Table 7. Means and Effect Sizes for Baseline Stability and Baseline vs Placebo comparisons for the PIRS-20.

Group	Timepoint	Baseline 1	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup> $d_{av}$
		Mean	Mean	Difference	LL	UL		
Group 1	Baseline 1 vs Baseline 2	30	23.67	6.33	-1.72	-0.08	89%	-0.92
	Baseline 1 vs Placebo 1	30	21.33	8.67	-2.51	0.19	95%	-1.2
Group 2	Baseline 1 vs Baseline 2	30.2	34	-3.8	x	x	68%	0.35
	Baseline 1 vs Placebo 1	30.2	31	-0.8	x	x	54%	0.07
	Baseline 1 vs Placebo 2	30.2	20.4	9.8	x	x	90%	-1.06
Group 3	Baseline 1 vs Baseline 2	27.67	32.5	-4.83	-0.11	1.04	73%	0.48
	Baseline 1 vs Placebo 1	27.67	21	6.67	-1.78	0.39	79%	-0.72
	Baseline 1 vs Placebo 2	27.67	16.83	10.84	-2.64	0.23	89%	-1.25
	Baseline 1 vs Placebo 3	x	x	x	x	x	x	x

Note: x = non-computable

a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

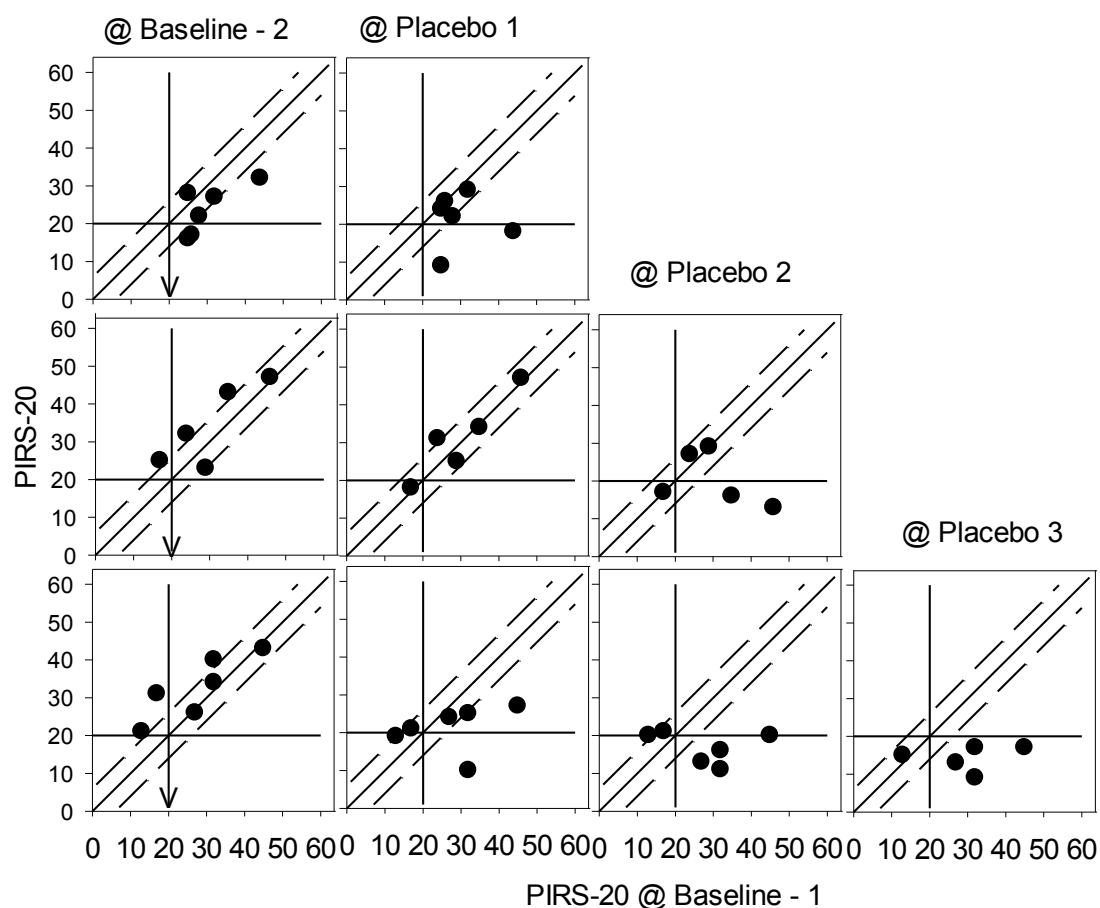


Figure 11. Modified Brinley plots showing baseline stability of insomnia symptoms and the placebo response for each of the three groups as measured by the PIRS-20. The top panel represents phase-length group 1 (5 days placebo); the middle panel represents phase-length group 2 (9 days placebo); and the bottom panel represents phase-length group 3 (14 days placebo).

Figure 12 (see below) shows the micronutrient treatment response relative to baseline one for each group. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 8 below. Because different participants have different durations of exposure to the placebo, the mean placebo response was computed for each participant and used to represent the overall placebo response for that individual. The top five plots represent the treatment response for phase-length group one. The initial plot presenting baseline one vs mean placebo shows the majority of participants show little mean level of change in their initial and mean placebo PIRS-20 scores, with only two reducing their scores below the clinical cut-off line. The CLES shows that the probability of participant's PIRS-20 scores being reduced at mean placebo compared to initial baseline is 95%; however,  $d$  is not reliably different from zero. Over the course of the next four plots a reduction

in PIRS-20 scores is seen, and by the end of treatment all participants' scores are reduced to below the clinical cut-off and display reliable positive change. The CLES shows 100% reduction; and the  $d_{av}$  ES is large and reliable (effect size magnitudes are interpreted using Cohen's (Cohen, 1992) criteria whereby 0.2 indicates a small effect, 0.5 a medium effect and 0.8 a large effect).

The middle four plots represent the treatment response for phase-length group 2. The initial plot presenting baseline 1 vs mean placebo shows that participants display little mean change in PIRS-20 scores with four out of five participants above the clinical cut-off. Over the next three plots, PIRS-20 scores scatter around the line of no change, and by the end of treatment one participant reduced their PIRS-20 score to below the clinical cut-off, and demonstrates reliable positive change. The CLES shows 75% reduction; however, as 95% CI's on  $d$  for this group were non-computable, it cannot be determined whether the mean change was reliable.

The bottom three plots represent the treatment response for phase-length group three. The initial plot presenting baseline 1 vs mean placebo shows the placebo response demonstrated by this group. Additionally, the CLES shows 86% reduction, but  $d$  is not reliably different from zero. The next plot demonstrates that participant's scores continue to decrease by week four with all scores below the clinical cut-off line. The CLES shows 98% reduction; and the  $d_{av}$  ES is large and reliable. By the end of treatment, one participant's score deviated above the clinical cut-off line demonstrating reliable deterioration, and four participants' scores remained in the non-clinical range. The CLES shows 96% reduction; however  $d$  is not reliably different from zero. Notably, this overall effect is due to the deterioration in score of the one participant, who was experiencing a bad sinus infection at the end of treatment assessment, which disrupted sleep.

Table 8. Means and Effect Sizes for Baseline 1 vs later score comparisons for each group treatment response on the PIRS-20 Stability and Baseline vs Placebo comparisons for the PIRS-20.

Group	Timepoint	Baseline 1	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup>
		Mean	Mean	Difference	LL	UL		$d_{av}$
Group 1	Baseline 1 vs Mean Placebo	30	21.33	8.67	-2.51	0.19	95%	-1.2
	Baseline 1 vs Treatment Day 9	30	22.67	7.33	-2.24	-0.05	93%	-1.18
	Baseline 1 vs Treatment Day 14	x	x	x	x	x	x	x
	Baseline 1 vs Treatment Week 4	30	17.5	12.5	-2.76	0.18	95%	-1.33
	Baseline 1 vs Treatment End	30	10.67	19.33	-5.32	-0.67	100%	-3.04
Group 2	Baseline 1 vs Mean Placebo	30.2	25.7	4.3	x	x	71%	-0.53
	Baseline 1 vs Treatment Day 14	30.2	21.8	4.5	x	x	84%	-0.75
	Baseline 1 vs Treatment Week 4	30.2	19.8	10.4	x	x	91%	-0.99
	Baseline 1 vs Treatment End	30.2	24.4	5.8	x	x	75%	-0.51
Group 3	Baseline 1 vs Mean Placebo	27.67	17.59	10.8	-2.49	0.22	86%	-1.17
	Baseline 1 vs Treatment Week 4	27.67	10	17.67	-3.76	-0.07	98%	-1.97
	Baseline 1 vs Treatment End	27.67	13.5	14.7	-3.01	0.39	96%	-1.39

Note: x = non-computable

a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

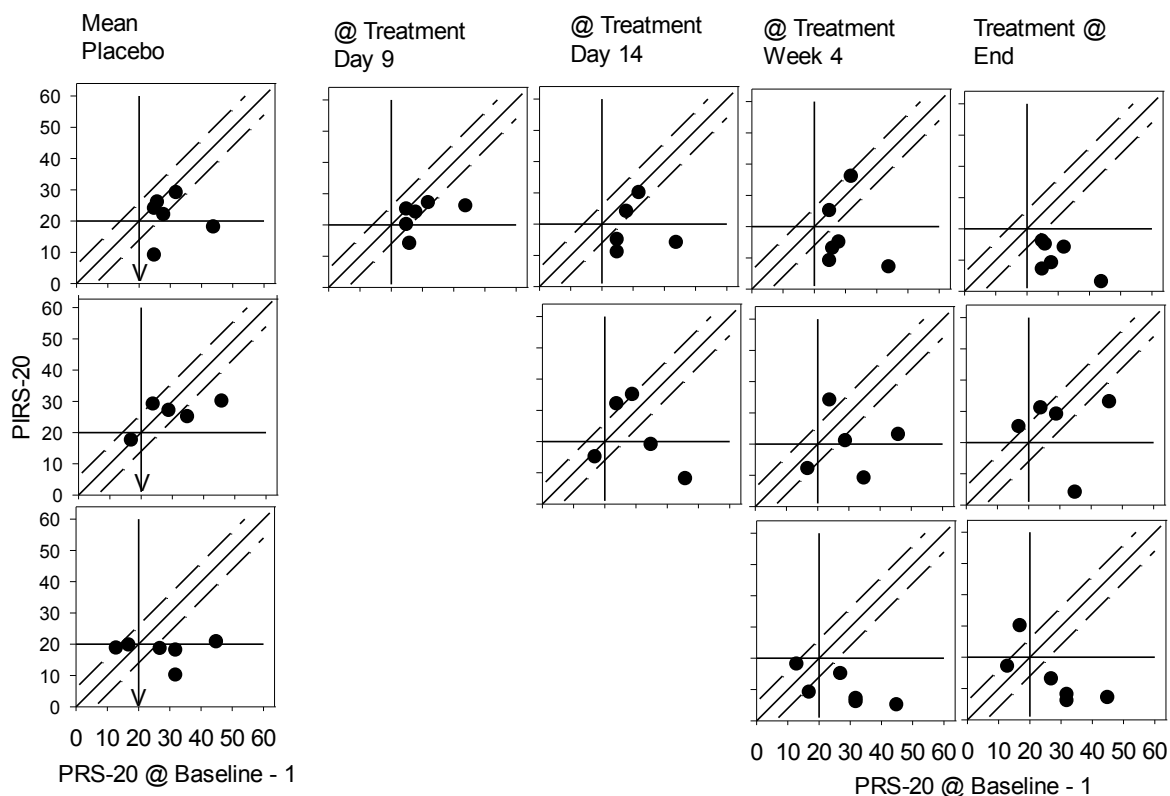


Figure 12. Modified Brinley plots showing the effect of the micronutrient intervention on insomnia as measured by the PIRS-20 for each of the three groups.

Figure 13 (see below) shows the effect of the micronutrient treatment on all participants over the treatment phase, relative to scores at initial baseline (the top panel), and relative to mean



placebo (middle panel) in order to detect any treatment effect of micronutrients over and above the effect of placebo. The bottom panel shows the follow-up data relative to scores at the end of treatment to examine the durability of any effect. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 9 below. The initial four plots present PIRS-20 scores vs mean placebo, treatment week 4, end of treatment and follow-up relative to initial baseline 1 scores. Of these, the first plot presenting PIRS-20 scores at baseline 1 vs mean placebo shows that there was a strong placebo effect as six participants reduced their scores to either at or below the clinical cut-off line and displayed reliable positive change. The CLES shows 89% reduction; and the  $d_{av}$  ES is large and reliable. By week four it becomes clear that the treatment effect is greater than the placebo effect as participants' PIRS-20 scores reduce further, with nine participants both below the clinical cut-off line and demonstrating reliable positive change. By the end of treatment it further becomes clear that participants have formed two groups - there is a group of responders and a group of non-responders. Twelve participants scores fall below the clinical cut-off line, and 11 of these demonstrate reliable positive change. Moreover, the CLES shows 97% reduction at treatment end; and the  $d_{av}$  ES's are both large and reliable at week four and end of treatment. At follow-up the two groups of responders and non-responders is still evident, and although overall participants scores have attenuated, reduction in PIRS-20 scores remains at follow-up as eight participants fall below the clinical cut-off line and also demonstrate reliable positive change. Furthermore, the CLES shows 89% reduction; and the  $d_{av}$  ES is large and reliable.

The middle panel of four plots present PIRS-20 scores vs mean baseline, treatment week 4, end of treatment and follow-up relative to mean placebo scores. The initial plot presenting PIRS-20 scores at mean placebo vs mean baseline show all participants but one have PIRS-20 scores in the clinical range. Over the course of the next two plots a reduction in PIRS-20 scores is shown, and by the end of treatment, 12 participants have reduced their PIRS-20 scores below the clinical cut-off line compared to their mean placebo score, with eight of these demonstrating reliable positive change. The CLES shows that the probability of participant's PIRS-20 scores

being reduced at week four and at end of treatment compared to mean placebo is 81% and 78% respectively; the respective  $d_{av}$  ES's are medium-large and medium and were both reliable. By follow-up PIRS-20 scores have attenuated; however, 14 participants scores are either at or below the clinical cut-off line, with five participants demonstrating reliable positive change. The CLES shows 61% reduction; but  $d$  is not reliably different from zero. Additionally, a group of responders and non-responders is evident at the end of treatment and follow-up relative to mean placebo, as was the case when change was viewed relative to initial baseline scores.

The bottom panel plot shows change in PIRS-20 scores at follow-up relative to those at the end of treatment. Overall, participants' PIRS-20 scores attenuated at follow-up in comparison to end of treatment, with five participants scores sitting at the clinical cut-off line and two participants PIRS-20 scores falling well above the clinical cut-off and demonstrating reliable deterioration. Four participants maintained PIRS-20 scores in the non-clinical range and demonstrated reliable positive change. The CLES shows 65% reduction; but  $d$  is not reliably different from zero.

Overall, Figure 13 shows that although a placebo effect was seen, there was an additional effect of treatment by micronutrients.

Table 9. Means and Effect Sizes for Timepoint 1 vs later score comparisons for all groups combined on the PIRS-20

Group	Timepoint	Timepoint 1	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup>
		Mean	Mean	Difference	LL	UL		$d_{av}$
Combined Group	Baseline 1 vs Mean Placebo	29.24	21.29	7.95	-1.68	-0.28	89%	-0.99
	Baseline 1 vs Treatment Week 4	29.24	15.53	13.71	-2.3	-0.53	97%	-1.44
	Baseline 1 vs Treatment End	29.24	15.71	13.53	-2.26	-0.45	97%	-1.37
	Baseline 1 vs Follow-up	29.24	18.88	10.36	-1.71	-0.18	89%	-0.96
Combined Group	Mean Placebo vs Mean Baseline	21.29	29.53	-8.26	0.38	1.81	92%	1.11
	Mean Placebo vs Treatment Week 4	21.29	15.53	5.76	-1.29	-0.14	81%	-0.72
	Mean Placebo vs Treatment End	21.29	15.71	5.58	-1.25	-0.06	78%	-0.66
	Mean Placebo vs Follow-up	21.29	18.88	2.41	-0.88	0.38	61%	-0.25
Combined Group	Treatment End vs Follow-up	15.71	18.88	-3.17	-0.44	1	65%	0.29

Note: a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

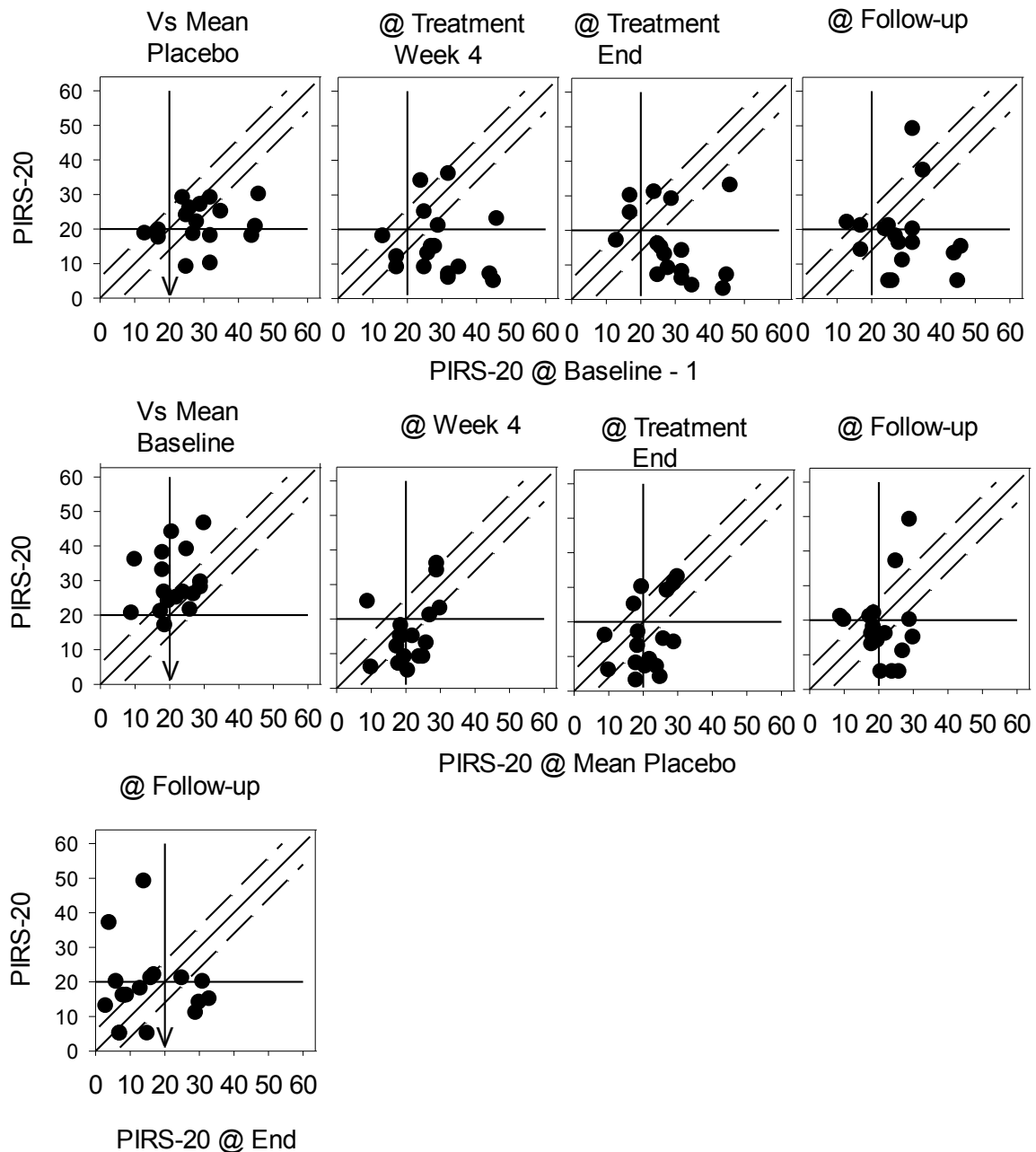


Figure 13. Modified Brinley plots showing the effect of the micronutrient intervention on insomnia in all three groups combined as measured by the PIRS-20.

Table 10 below presents CLES, Cohen's  $d_{av}$ , 95% CI's on  $d$  and mean change over the course of the intervention for the four participants who continued to take the micronutrients after the intervention concluded. The CLES show that by follow-up, the probability of participant's PIRS-20 scores being reduced at follow-up compared to initial baseline and mean placebo are 88% and 69% respectively. Although the 95% CI's on  $d$  could not be computed and thus reliability of mean level of change cannot be determined, the  $d_{av}$  ES's are generally moderate to

large throughout the micronutrient phase and at follow-up. In terms of follow-up relative to treatment end, the CLES shows that the probability of participant's PIRS-20 scores being reduced at follow up compared to treatment end is 54%; however, the 95% CI's on  $d$  could not be computed and thus reliability of mean level of change cannot be determined.

Table 10. Means and Effect Sizes for Timepoint 1 vs later score comparisons on the PIRS-20 for participants who continued micronutrients after the intervention concluded.

Group	Timepoint	Timepoint 1	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup> $d_{av}$
		Mean	Mean	Difference	LL	UL		
Continued Micronutrients	Baseline 1 vs Mean Placebo	35.75	28.88	6.87	x	x	72%	-0.71
	Baseline 1 vs Treatment Week 4	35.75	11.5	24.25	x	x	99%	-2.2
	Baseline 1 vs End of Treatment	35.75	18.5	17.25	x	x	95%	-1.2
	Baseline 1 vs Follow-up	35.75	19.75	16	x	x	88%	-0.9
Continued Micronutrients	Mean Placebo vs Follow-up	28.88	19.75	9.13	x	x	69%	-0.64
Continued Micronutrients	Treatment End vs Follow-up	18.5	19.75	-1.25	x	x	54%	0.02

Note: x = non-computable

a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

### 3.3.2 Secondary measures

The following figures show the effect of the intervention on depression, anxiety and stress symptoms as measured by the DASS-21 over the course of the intervention relative to baseline 1. Table 11 presents Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES for DASS-21 scores over the intervention relative to baseline 1. When interpreting the results, it is important to remember that for all three subscales (depression, anxiety and stress), the majority of participants were below the clinical cutoffs at initial baseline, thus indicating that the current sample was essentially non-clinical for these measures.

Table 11. Means and Effect Sizes for Baseline 1 vs later score comparisons for the DASS-21.

Timepoint	Subscale	Baseline 1	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup> $d_{av}$
		Mean	Mean	Difference	LL	UL		
Baseline 1 vs Baseline 2	Depression	2.29	2.76	-0.47	-0.28	0.68	61%	0.2
	Anxiety	2.71	3.12	-0.41	-0.18	0.52	59%	0.18
	Stress	6.47	6.94	-0.47	-0.35	0.6	57%	0.13
	Total	11.47	12.82	-1.35	-0.23	0.64	61%	0.2
Baseline 1 vs Mean Placebo	Depression	2.29	1.82	0.47	-0.7	0.3	61%	-0.21
	Anxiety	2.71	1.99	0.72	-0.7	-0.01	68%	-0.36
	Stress	6.47	5.56	0.91	-0.82	0.29	64%	-0.27
	Total	11.47	10.41	1.06	-0.57	0.22	59%	-0.18
Baseline 1 vs Treatment Week 4	Depression	2.29	1.06	1.23	-1.3	0.09	76%	-0.61
	Anxiety	2.71	1.71	1	-0.96	0.04	72%	-0.47
	Stress	6.47	4.65	1.82	-1.18	0.22	74%	-0.49
	Total	11.47	7.41	4.06	-1.33	0.05	81%	-0.65
Baseline 1 vs Treatment End	Depression	2.29	1.88	0.41	-0.8	0.46	59%	-0.17
	Anxiety	2.71	1.41	1.3	-1.3	-0.13	82%	-0.73
	Stress	6.47	3.94	2.53	-1.47	0.09	83%	-0.7
	Total	11.47	7.24	4.23	-1.4	0.06	82%	-0.68
Baseline 1 vs Follow-up	Depression	2.29	2.06	0.23	-0.8	0.64	54%	-0.08
	Anxiety	2.71	1.71	1	-1.08	0.17	73%	-0.46
	Stress	6.47	5.71	0.76	-0.82	0.42	61%	-0.21
	Total	11.47	9.47	2	-0.92	0.33	65%	-0.3

Note: a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

Figure 14 assess baseline stability of DASS-21 measures and shows the analysis of change in these symptoms over the one week baseline period (baseline 1 vs baseline 2). For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 11. The top two plots show that depression and anxiety were relatively stable and show little change, with just one participant above the clinical cut-off for anxiety and demonstrating reliable deterioration. In terms of stress, scores are widely scattered around the line of no change with the thirteen deviating below this line and nine exceeding the lower RCI boundary. Overall however, the fourth plot indicates that total DASS-21 scores did not significantly improve over the one-week baseline, which is confirmed as all 95% CI's on  $d$  cross zero.

### DASS-21 Baseline 1 vs Baseline 2

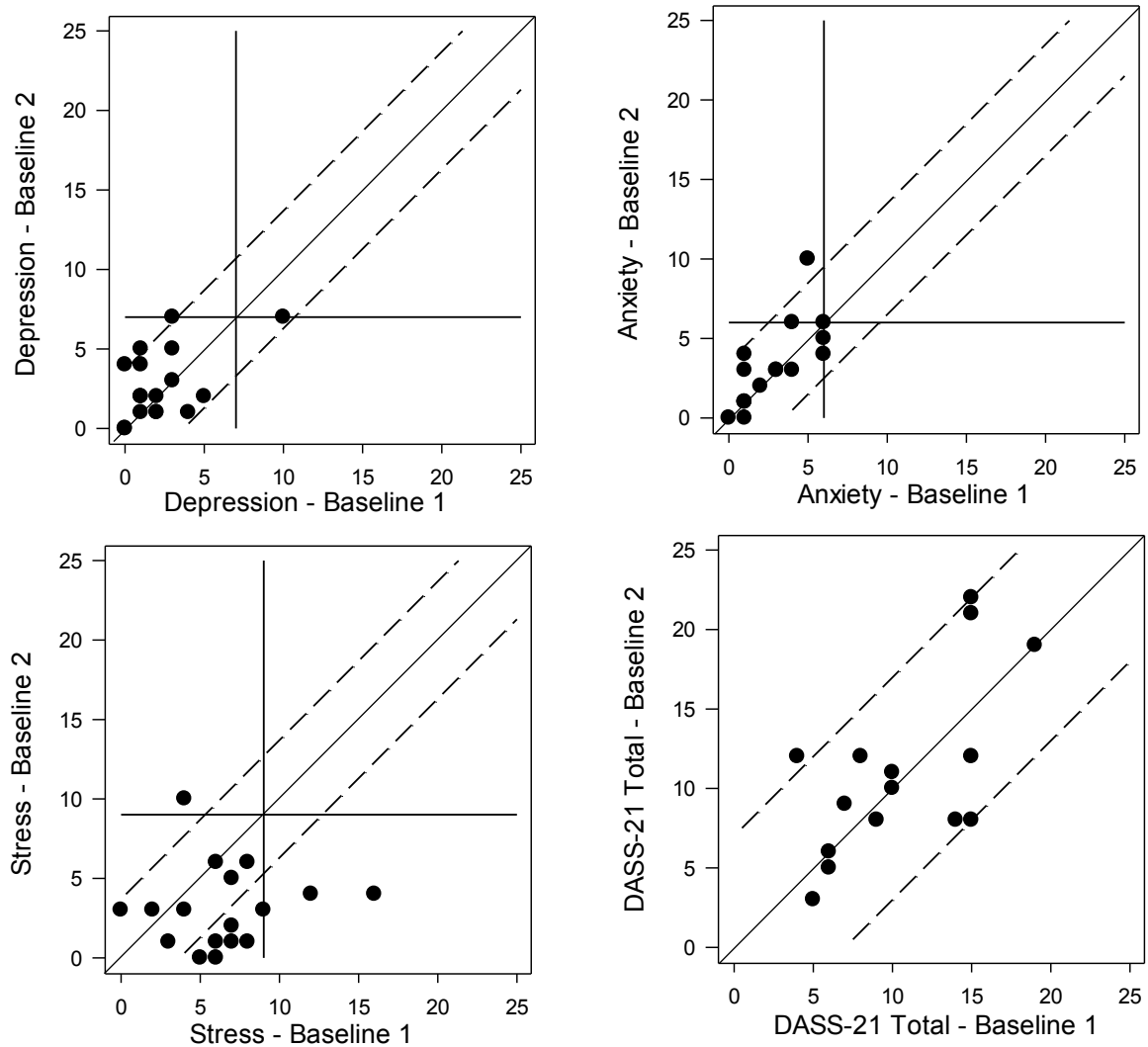
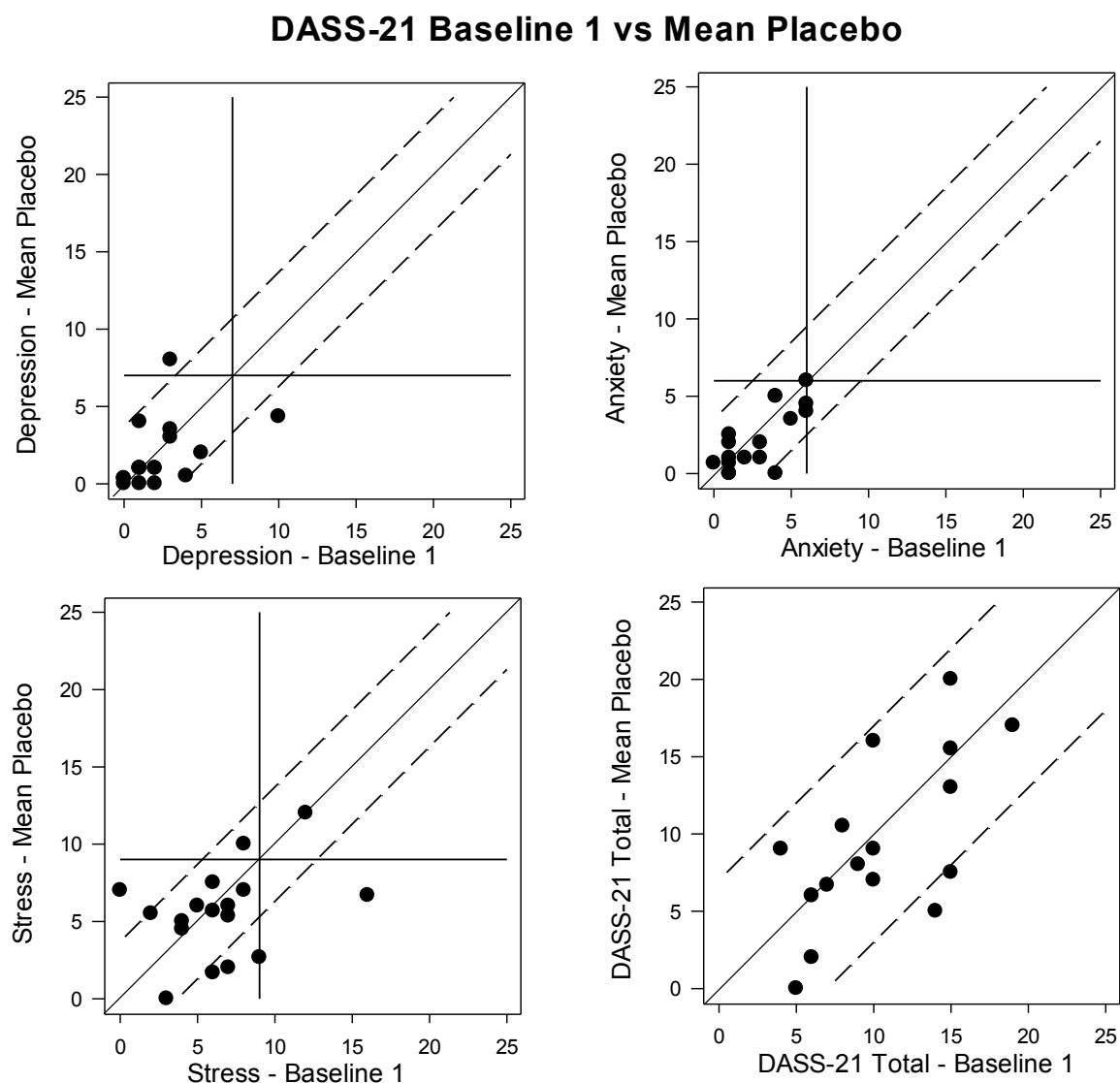


Figure 14. Modified Brinley plots showing baseline stability of depression, anxiety and stress symptoms as measured by the DASS-21.

Figure 15 shows whether participants displayed a change in depression, anxiety and stress symptoms over the placebo phase period as compared to baseline 1. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 11. The initial plot displaying change in depression scores indicates that little mean change was seen, with only one participant reducing their depression score and demonstrating reliable positive change over the placebo period, and one participant increasing their depression score and demonstrating reliable deterioration. The second plot displaying anxiety scores does not indicate much change; however, the CLES shows that the probability of participant's anxiety scores being reduced at mean placebo compared to initial

baseline is 68%; and the  $d_{av}$  ES is small and statistically reliable. The third plot displaying change in stress symptoms indicates that a small placebo effect was seen for stress, as shown by three participants reducing their scores over the placebo period and demonstrating reliable positive change. The CLES shows 64% reduction, but  $d$  is not reliably different from zero. The fourth plot presenting total DASS-21 scores at initial baseline relative to mean placebo scores indicates that overall there was a very slight placebo effect with nine participants scores deviating below the line of no change, and only two demonstrating reliable positive change. The CLES shows 59% reduction, but  $d$  is not reliably different from zero.



*Figure 15.* Modified Brinley plots showing the change in depression, anxiety and stress at mean placebo relative to baseline 1 score as measured by the DASS-21.

Figure 16 shows the effect of the intervention on depression, anxiety and stress symptoms at week 4 relative to baseline 1. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 11. The plot presenting depression scores at week 4 relative to baseline 1 indicates that by this stage of the intervention, all participants are below the clinical cut-off score, with two participants reducing their scores to demonstrate reliable positive change. It is important to remember, however, that the majority of participants' scores were below the clinical cut-off at baseline. The plot presenting change in anxiety scores shows all but two participants' scores are below the clinical cut-off line, with two participants reducing their scores to demonstrate reliable positive change. In terms of stress, although scores are scattered above and below the line of no change, the majority of scores deviate below it with four participants demonstrating reliable positive change. The final plot presenting the effect of the intervention on total DASS-21 scores at week 4 relative to baseline 1 displays a range of scatter above and below the line of no change. Seven participants reduced their scores below the line of no change, with four participants demonstrating reliable positive change. The CLES shows that the probability of participant's depression, anxiety, stress and total DASS-21 scores being reduced at treatment week 4 compared to initial baseline is 76%, 72%, 74% and 81% respectively; the respective  $d$ 's however, were not reliably different from zero.



### DASS-21 Baseline 1 vs Treatment Week 4

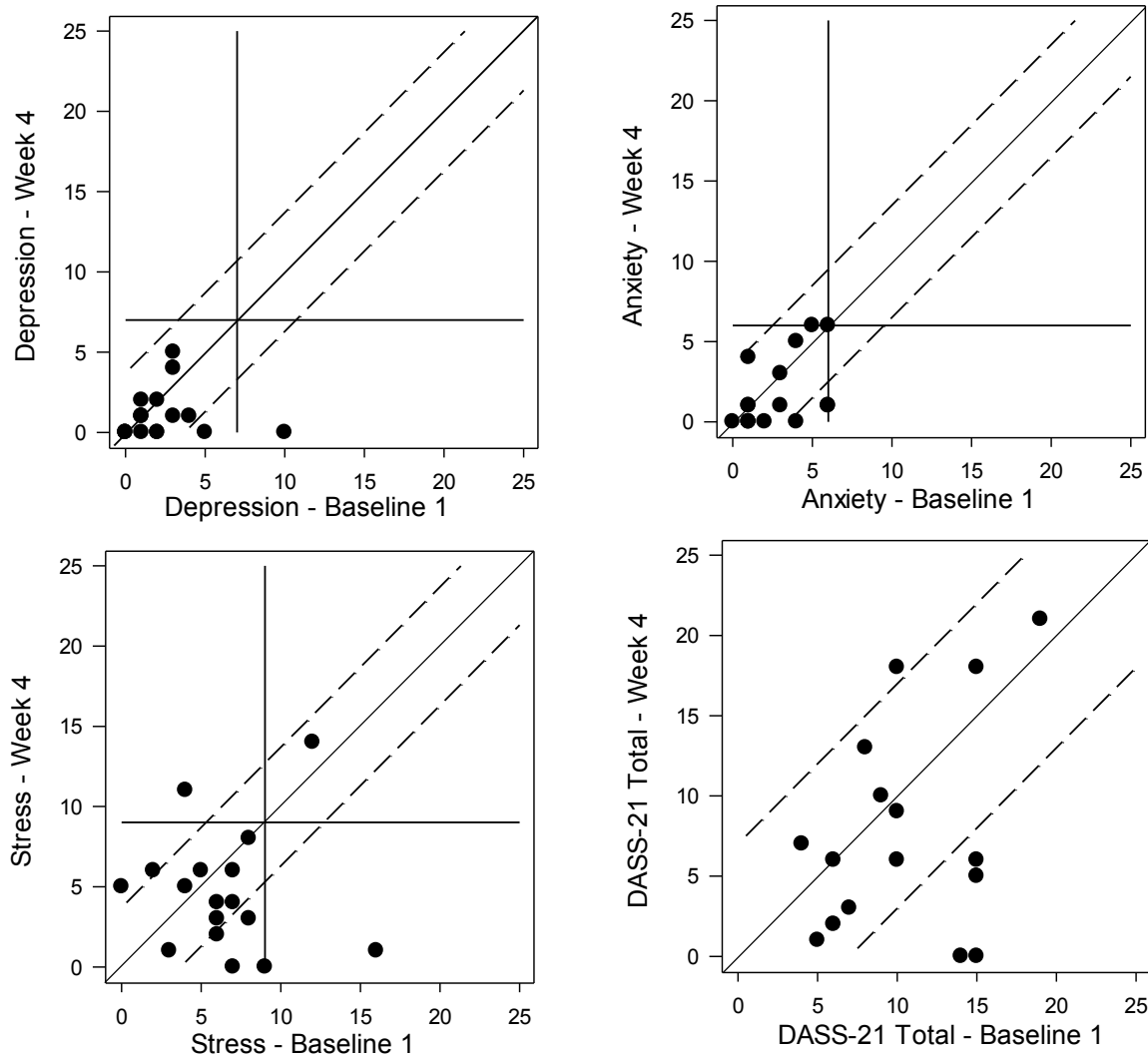


Figure 16. Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at week 4 relative to baseline 1 score as measured by the DASS-21.

Figure 17 shows the effect of the intervention on depression, anxiety and stress symptoms at the end of the intervention relative to baseline 1. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 11. The initial plot presenting baseline 1 vs treatment end for depression, shows slight attenuation in scores in comparison to treatment at week 4, with two participants sitting on the clinical cut-off line. However four participants reduced their scores to below the line of no change, with two demonstrating reliable positive change. The CLES shows that the probability of participant's depression scores being reduced at end of treatment compared to initial baseline was 59%; but  $d$  was not reliably different from zero. In terms of anxiety, this plot

shows a trend toward a decrease in anxiety symptoms with all participants in the non-clinical range. The CLES shows 82% reduction; and the  $d_{av}$  ES is medium-large and statistically reliable. The third plot presenting change in stress scores at baseline 1 relative to treatment end shows a decrease in stress as 10 participants fall below the line of no change, with six of these demonstrating reliable positive change. The CLES shows 83% reduction, but  $d$  is not reliably different from zero. Both the plot presenting change in stress scores and the final plot presenting change in total DASS-21 scores show that at the end of the intervention there were a group of responders and a group on non-responders, as demonstrated by the clusters of data points above and below the line of no change. The final plot shows that 10 participants reduced their scores below the line of no change with four demonstrating reliable positive change. The CLES shows 82% reduction, but  $d$  is not reliably different from zero.

### DASS-21 Baseline 1 vs Treatment End

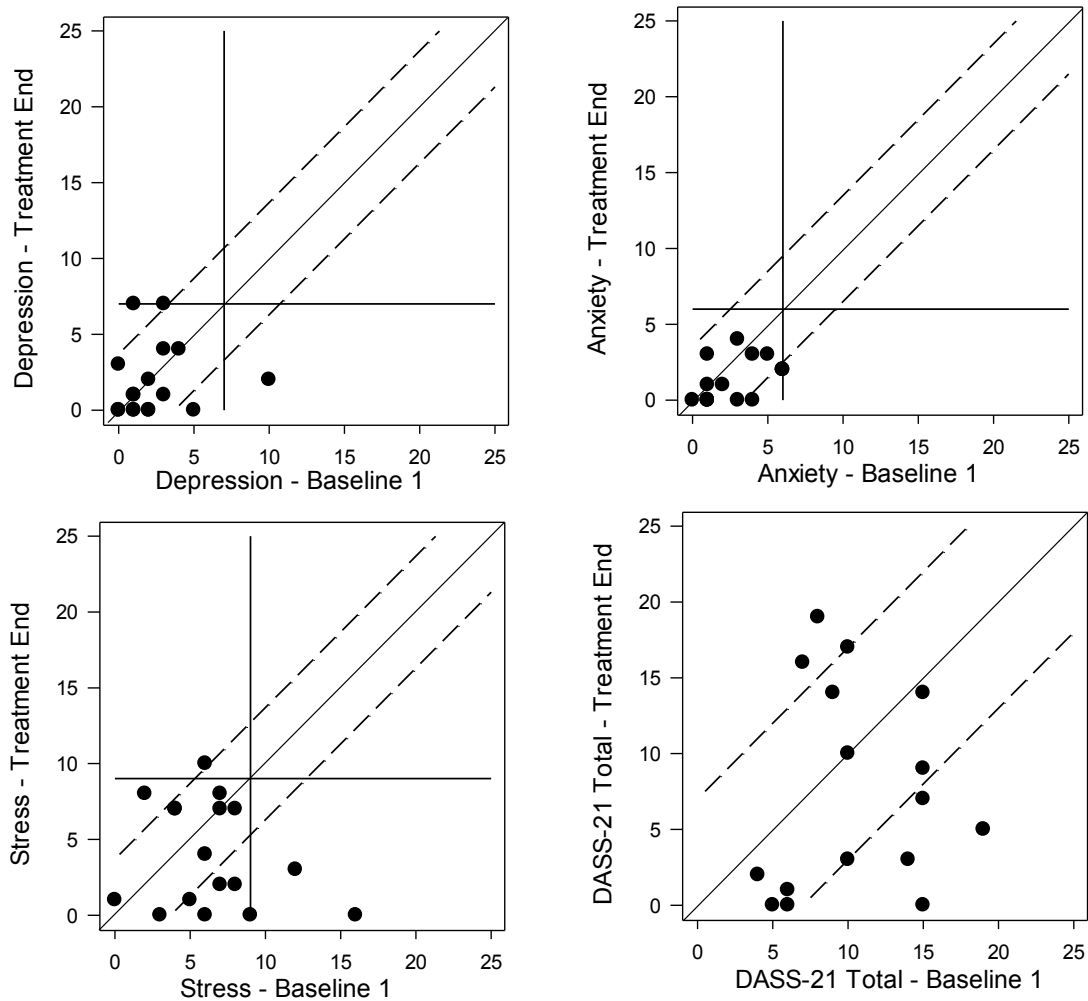
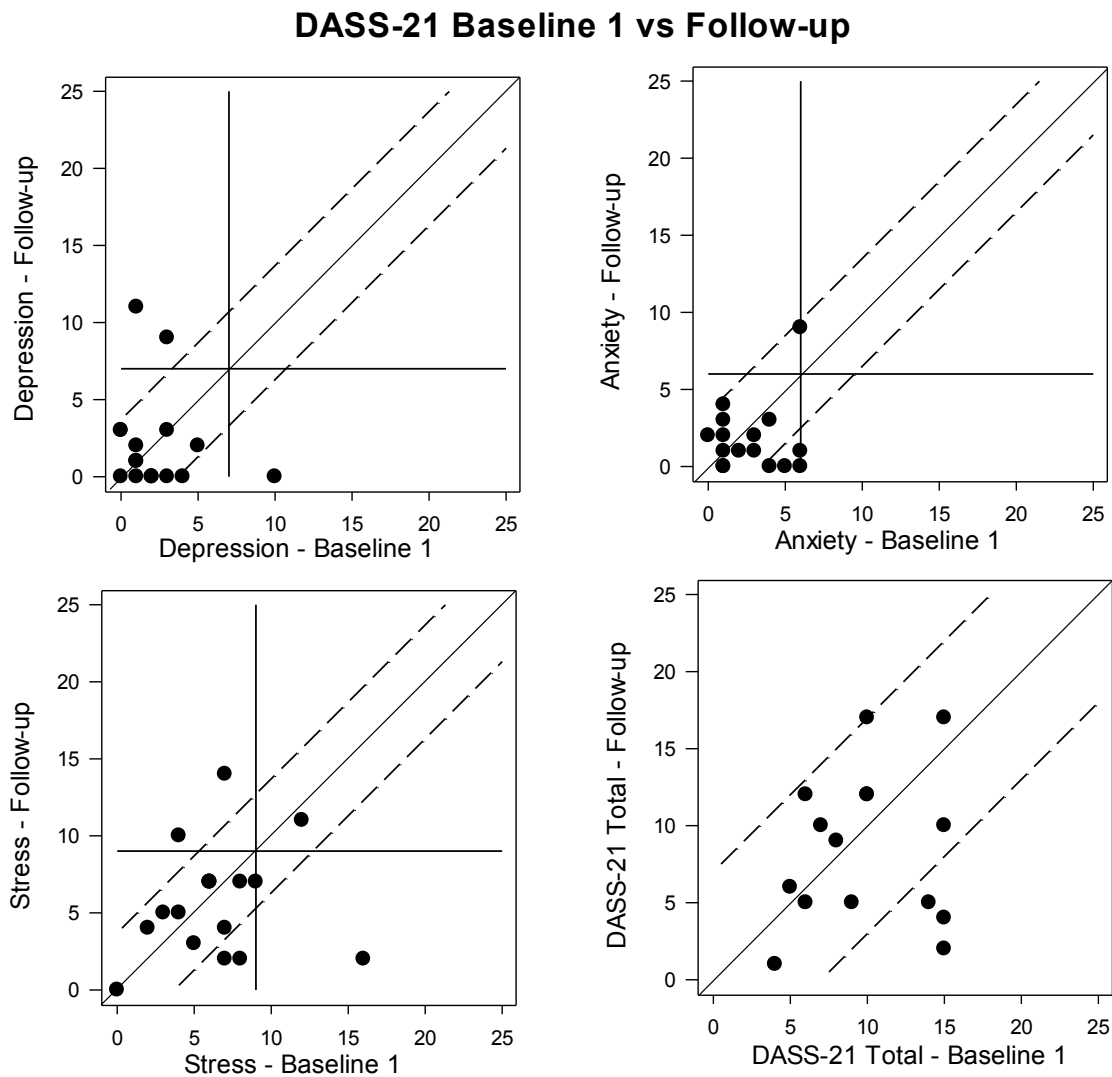


Figure 17. Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at end of treatment relative to baseline 1 score as measured by the DASS-21.

Figure 18 presents depression, anxiety and stress scores for baseline 1 relative to follow-up. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 11. The initial plot presenting depression scores for baseline 1 relative to follow-up shows that some participants continued to reduce their scores, as five participants scores deviated below the line of no change; and two deteriorated into the clinical range. In terms of anxiety, the second plot shows five participants' scores deviated above the line of no change, with one participant's score increasing above the clinical cut-off at follow-up. Of five participants who reduced their scores below the line of no change, three demonstrated reliable positive change. The third plot demonstrates that at follow-up stress scores changed for the worse, with three participants entering the clinical range. The

increase in scores is most evident in the final plot presenting change in total DASS-21 scores, with just six participants deviating below the line of no change and three demonstrating reliable positive change. The CLES shows that the probability of participant's depression, anxiety, stress and total DASS-21 scores being reduced at follow-up compared to initial baseline was 54%, 73%, 61% and 65% respectively; the respective  $d$ 's however, are not reliably different from zero.



*Figure 18.* Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at follow-up to baseline 1 score as measured by the DASS-21.

The following figures show the effect of the intervention on depression, anxiety and stress symptoms as measured by the DASS-21 over the course of the intervention relative to the mean placebo effect. Table 12 presents Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES for DASS-21 scores over the intervention relative to mean placebo.

Table 12. Means and Effect Sizes for Mean Placebo vs later score comparisons for the DASS-21.

Timepoint	Subscale	Mean Placebo	Later Score	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup>
		Mean	Mean	Difference	LL	UL		$d_{av}$
Mean Placebo vs Treatment Week 4	Depression	1.82	1.06	0.76	-0.97	0.16	70%	-0.41
	Anxiety	1.99	1.71	0.28	-0.55	0.28	57%	-0.14
	Stress	5.56	4.65	0.91	-0.71	0.18	64%	-0.27
	Total	9.72	7.41	2.31	-0.88	0.12	69%	-0.38
Mean Placebo vs Treatment End	Depression	1.82	1.88	-0.06	-0.6	0.66	51%	0.03
	Anxiety	1.99	1.41	0.58	-0.82	0.14	67%	-0.34
	Stress	5.56	3.94	1.62	-1.13	0.14	75%	-0.5
	Total	9.72	6.59	3.13	-1.01	0.19	71%	-0.41
Mean Placebo vs Follow-up	Depression	1.82	2.06	-0.24	-0.46	0.64	54%	0.09
	Anxiety	1.99	1.71	0.28	-0.8	0.53	57%	-0.14
	Stress	5.56	5.71	-0.15	-0.58	0.67	52%	0.04
	Total	9.72	8.88	0.84	-0.68	0.43	56%	-0.13

Note: a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

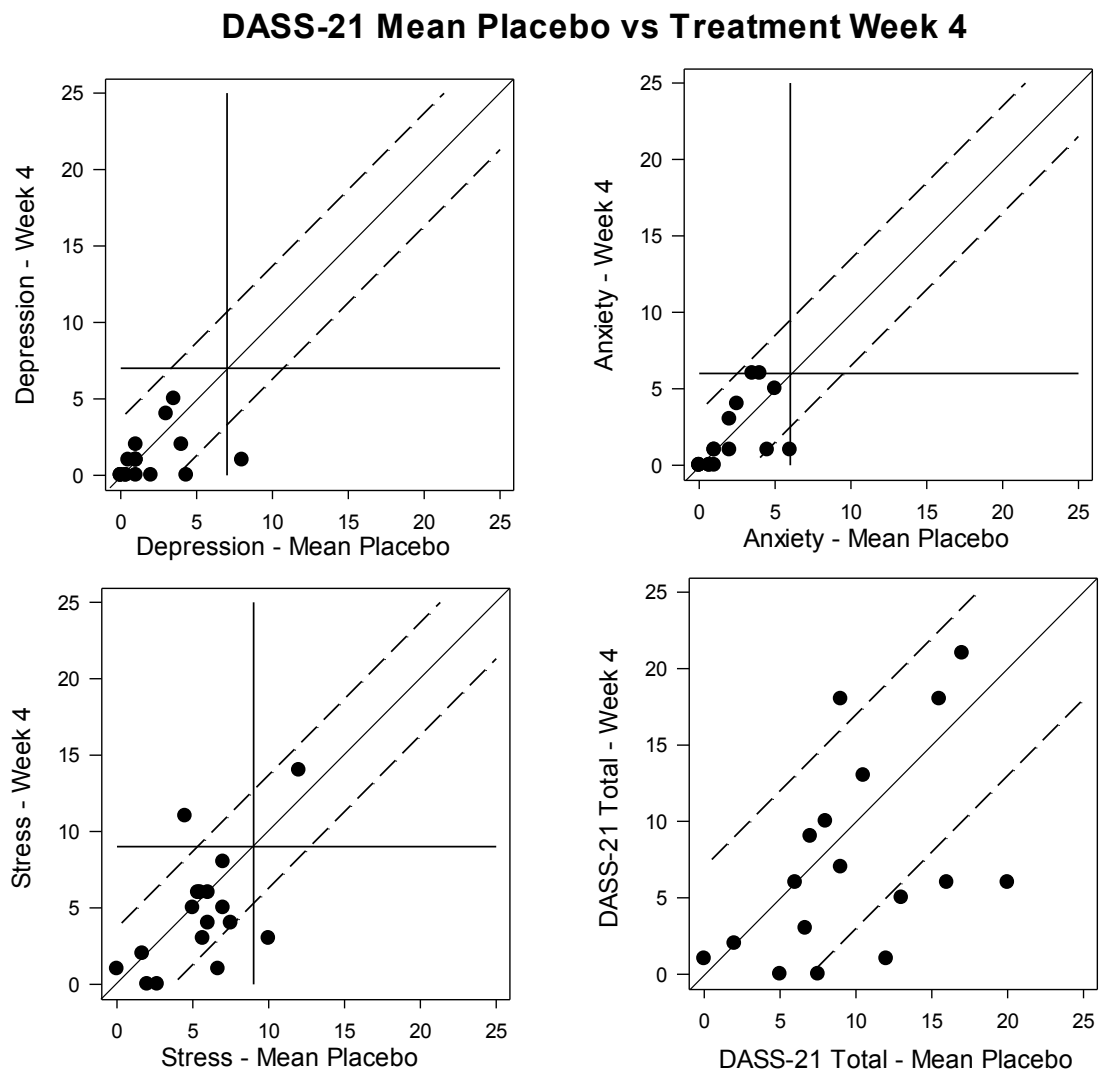
b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

Figure 19 presents depression, anxiety and stress scores at week 4 relative to mean placebo scores. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 12. The initial plot presenting mean placebo vs treatment at week 4 for depression scores shows that all participants were below the clinical cut-off line and two demonstrated reliable positive change in depressive symptoms. The second plot presenting mean placebo vs treatment at week 4 for anxiety scores shows that the majority of participants' scores fall below the clinical cut-off and lie closely around the line of no change. Two participants scores increased at week 4 and sit at the clinical cut-off line; and another two participants show a reduction in scores compared to their mean placebo score, with one demonstrating reliable positive change and one sitting on the RCI line. The CLES shows that the probability of participant's depression and anxiety scores being reduced at treatment week 4 compared to mean placebo was 70% and 57% respectively; the respective  $d$ 's however, were not reliably different from zero.

The third plot presenting mean placebo vs treatment at week 4 for stress scores shows that 14 participants scores are below the clinical cut off, with seven participants scores deviating below the line of no change and two demonstrating reliable positive change. Of the two participants above the clinical cut-off for stress, one participant shows reliable deterioration and

the other deviates just about the line of no change. The CLES shows 64% reduction, but  $d$  is not reliably different from zero. The fourth plot presents overall DASS-21 scores and shows that total scores scatter widely around the line of no change. Some participants display deterioration in scores at week 4 whereas five participants demonstrate reliable positive change in total score. The CLES shows 69% reduction, but  $d$  is not reliably different from zero.

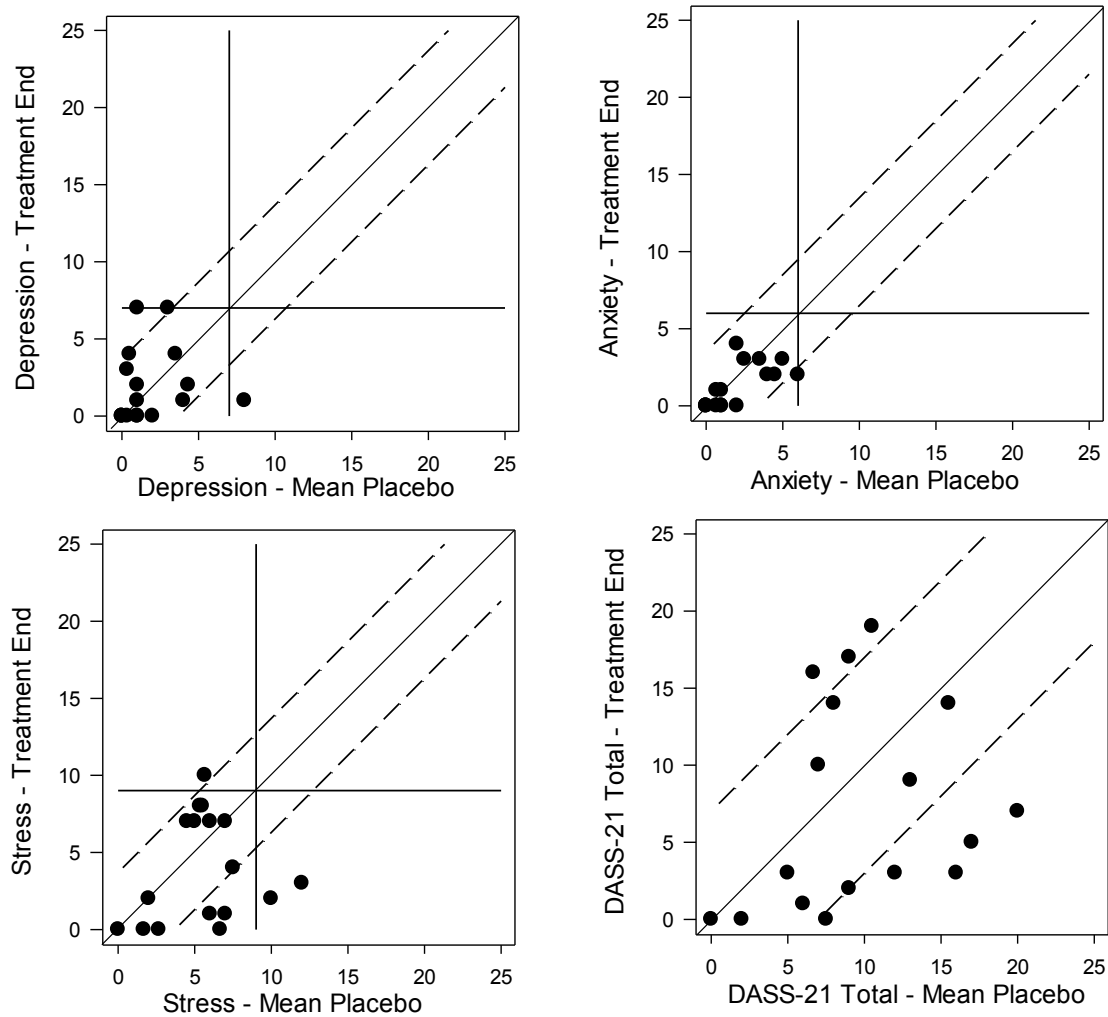


*Figure 19.* Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at week 4 relative to mean placebo score as measured by the DASS-21.

Figure 20 presents depression, anxiety and stress scores at end of treatment relative to mean placebo scores. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 12. The initial plot presenting mean placebo vs treatment end for depression scores shows little mean change at the

end of treatment relative to initial mean placebo depression scores was seen compared to initial mean placebo scores. Eleven participants scores fall below the clinical cut-off, with five reducing their scores below the line of no change, and one demonstrating reliable positive change. The CLES shows that the probability of participant's depression scores being reduced at end of treatment compared to mean placebo was 51% (i.e., at chance level) and  $d$  is not significantly different from zero. The second plot presenting anxiety scores shows little mean change at end of treatment relative to mean placebo, as twelve participants scores fall inside the RCI boundaries. Despite this, all scores are below the clinical cut-off, although the CLES = 67% and  $d$  was not significantly different from zero. The third plot presents stress scores at treatment end relative to mean placebo, and it can be seen that there is a group of responders and non-responders. Fifteen participants scores are below the clinical cut-off, and 8 participants deviate below the line of no change with five of these demonstrating reliable positive change. The CLES shows that the probability of participant's stress scores being reduced was 75% but  $d$  is not reliably different from zero. The final plot presents DASS-21 total scores, which shows there is again a group of responders and a group of non-responders. Overall, the plot shows a decrease in total scores at treatment end relative to placebo, with 11 participant's scores deviating below the line of no change, and six either at or below the lower boundary of the RCI. The CLES was 71%;  $d$  however, is not reliably different from zero.

### DASS-21 Mean Placebo vs Treatment End



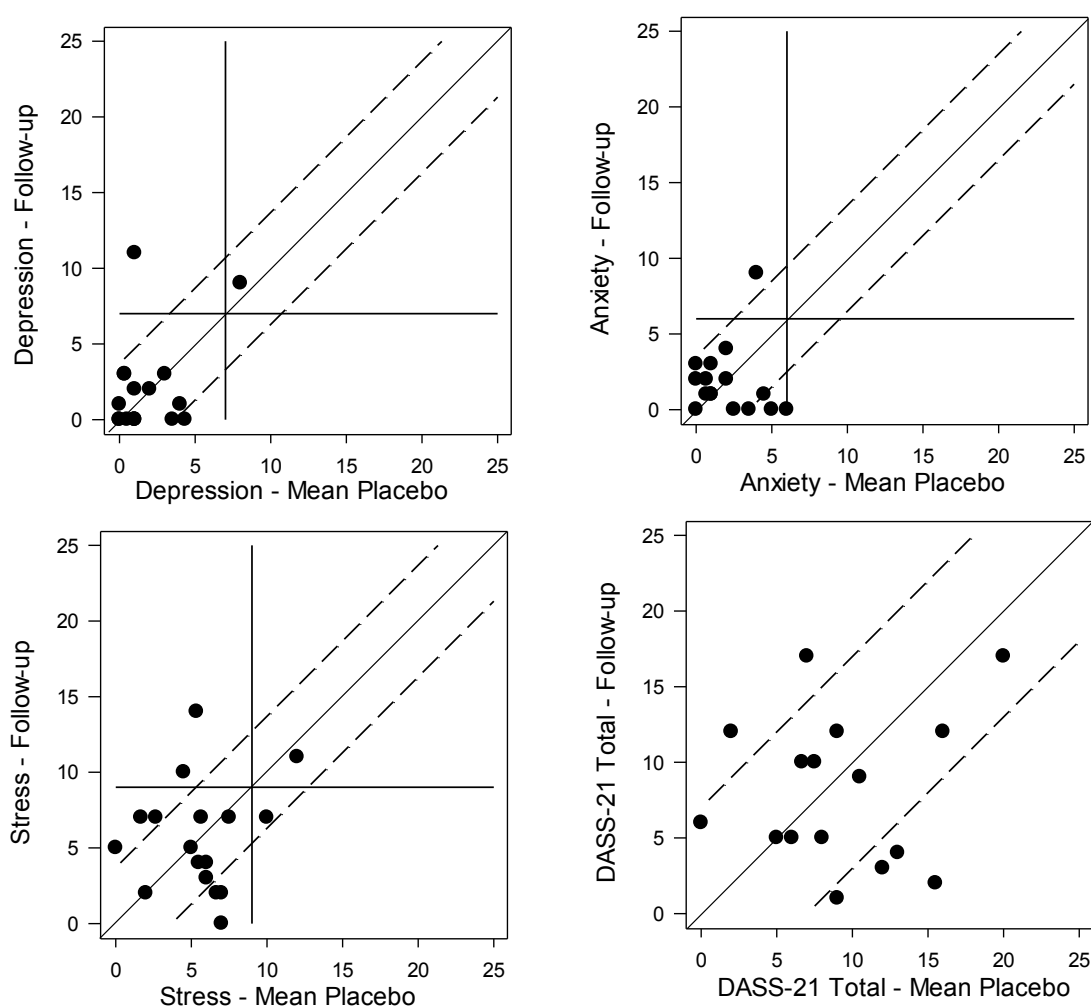
*Figure 20.* Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at end of treatment relative to mean placebo score as measured by the DASS-21.

Figure 21 presents depression, anxiety and stress scores at follow-up relative to mean placebo scores. For Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES see Table 12. The initial plot presenting depression scores at mean placebo vs follow-up shows little mean change; however, 11 participant's scores fall below the clinical cut-off line, and four participant's reduced their scores below the line of no change, with one demonstrating reliable positive change. The second plot presenting anxiety scores shows a small amount of mean change, with scores deviating both above and below the line of no change. One participant's score increases above the clinical cut-off in comparison to their mean placebo score. The remaining 14 participant's scores fall below the clinical cut-off with four of these either at or below the lower RCI boundary. The third plot



demonstrates an overall increase in stress scores at follow-up compared to mean plot, with three participants' stress scores increasing to clinical levels. The CLES shows that the probability of participant's depression, anxiety and stress scores reduced at follow-up compared to mean placebo was 54%, 57% and 52% respectively; the respective  $d$ 's however, were not reliably different from zero. The final plot demonstrates that overall DASS-21 scores increased, with a wide scatter around the line of no change. The CLES shows that the probability of participants' total DASS-21 scores being reduced at follow-up compared to mean placebo was 56%;  $d$  was not reliable.

### DASS-21 Mean Placebo vs Follow-up



*Figure 21.* Modified Brinley plots showing the effect of the micronutrient intervention on depression, anxiety and stress at follow-up relative to mean placebo score as measured by the DASS-21.

The following figure shows the effect of the intervention on emotional exhaustion (EE) and depersonalisation (DP) as measured by the MBI-ES. Table 13 presents Cohen's  $d_{av}$ , 95% CI's on  $d$  and CLES for MBI-ES scores at the end of treatment relative to initial baseline 1 score.

Table 13. *Means and Effect Sizes for Baseline 1 vs Treatment End for the MBI-ES*

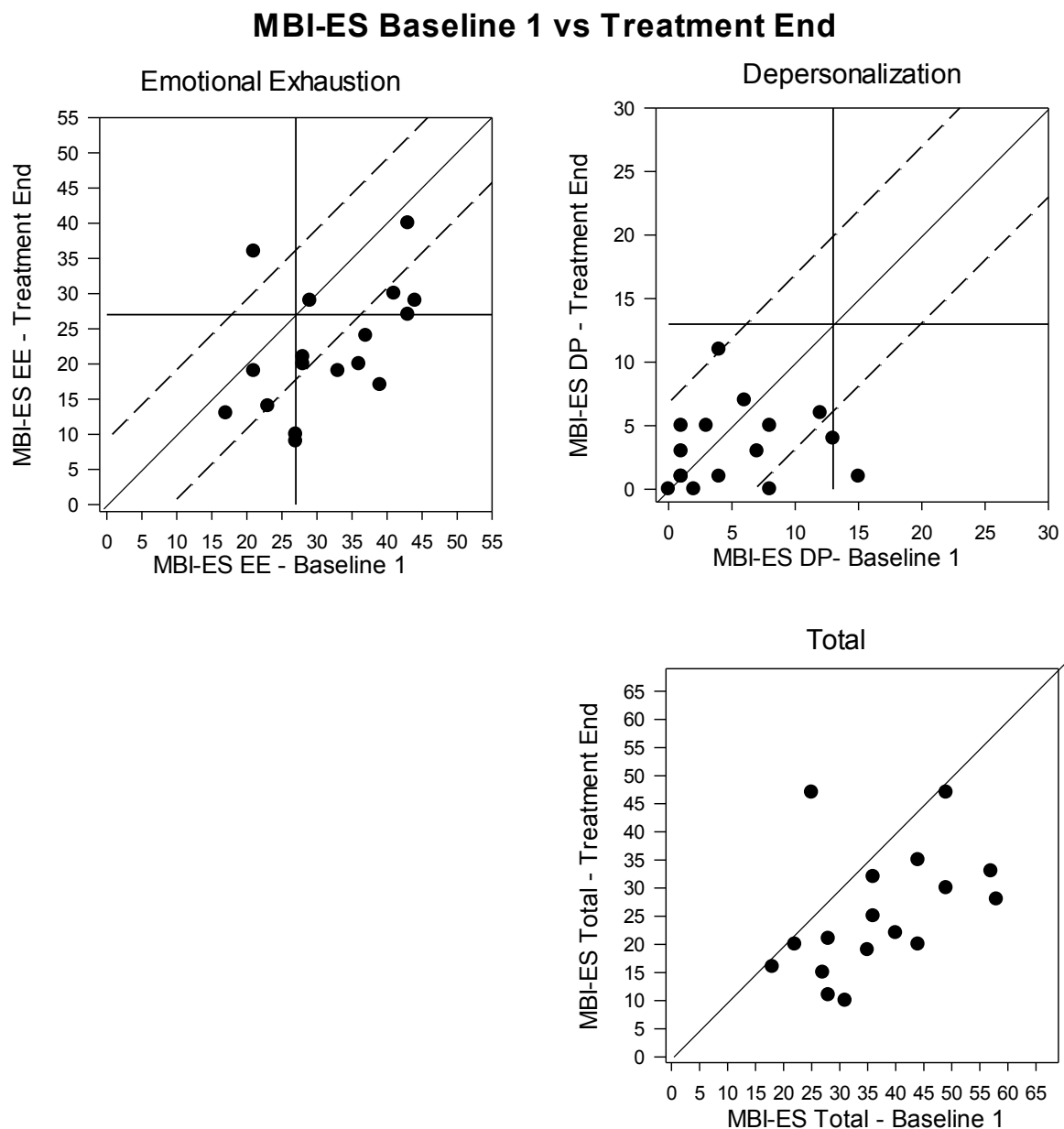
Timepoint	Subscale	Baseline 1	Treatment End	Mean	95% CI <sup>a</sup>		CLES <sup>b</sup>	Cohen's <sup>c</sup>
		Mean	Mean	Difference	LL	UL		$d_{av}$
Baseline 1 vs Treatment End	Emotional Exhaustion	31.59	22.18	9.41	-1.69	-0.46	93%	-1.08
	Depersonalization	5.29	3.18	2.11	-1.19	0.12	75%	-0.54
	Total	36.88	25.35	11.53	-1.61	-0.38	91%	-1.01

Note: a. 95% CI on  $d$  = 95% Confidence Interval on  $d$  (LL = Lower Limit; UL = Upper Limit)

b. CLES = Common Language Effect Size

c. Cohen's  $d_{av}$  = the effect size for within subject design

Figure 22 presents EE and DP scores at the end of treatment relative to baseline 1. As this measure was only completed at the beginning of baseline and end of intervention, only three Brinley plot comparisons are presented. The initial plot presenting the effect of the intervention on EE scores shows 10 participants' reduced their scores below the clinical cut-off, and six of these demonstrate reliable positive change. The CLES = 93% reduction; and  $d_{av}$  ES is large and statistically reliable. In terms of depersonalization, the second plot indicates no strong effect of the intervention was seen at end of treatment relative to baseline 1, with data points widely scattered around the line of no change. However, eight participants reduced their scores below the line of no change and three demonstrate reliable positive change. Additionally, the CLES shows 75% reduction, but  $d$  is not reliably different from zero. The final plot presenting MBI-ES total scores at the end of intervention relative to baseline 1 indicates that overall there was significant improvement in mean change of MBI-ES scores; the CLES 91% reduction;  $d_{av}$  ES is large and reliable, and 13/17 participants fall below the line of no change.



*Figure 22.* Modified Brinley plots showing the effect of the micronutrient intervention on emotional exhaustion and depersonalization at end of treatment relative to baseline 1 score as measured by the MBI-ES.

In summary, the results show that the majority of participants demonstrated a reliable and clinically significant decrease in insomnia severity, as well as demonstrating improvements on at least two aspects of sleep as measured by the CSD-M. Although a placebo effect was evident, there was an additional effect of the micronutrients overall. By the end of treatment, it becomes evident that the participants have split into two groups: five who did not respond and 12 who did. By follow-up, overall, no additional improvement is seen from the end of treatment to follow-up.

However, improvements obtained during the intervention still remain, as only a slight deterioration in scores is seen. Those that continued with the micronutrients after the intervention also show a slight deterioration in scores at follow-up compared to end of treatment.

In terms of anxiety, stress and depression scores, the majority of participants were in the non-clinical range on these scales at baseline; and no statistically significant reduction was seen in anxiety, stress and depression scores at end of treatment. At follow-up, overall no further improvement was seen, with the majority of participants' scores deteriorating back toward initial baseline. Additionally, a statistically significant reduction was seen in emotional exhaustion scores as measured by the MBI-ES, however, statistically significant change was not seen for depersonalization as scores were low to begin with.

## 4. Discussion

### 4.1 Discussion of Findings

The current sample reflected a group of Christchurch teachers working in earthquake-affected schools, who were experiencing clinically significant levels of chronic insomnia. A discussion of the findings relating to the innovative micronutrient intervention is presented below.

**Insomnia.** Overall, the results show that the micronutrient intervention was associated with improvements in insomnia symptoms relative to placebo. This primary hypothesis was supported in that the group mean insomnia severity rating (as measured by the PIRS-20) dropped from 29.4 at baseline to 15.71 at treatment end, with a large and statistically reliable effect size (Cohen's  $d_{av} = -1.37$ , CLES = 97%). The reliability of this result was further supported as 11 out of 17 participants experienced a clinically significant decrease in insomnia severity on the PIRS-20 (i.e., their scores dropped below the clinical cut-off).

Improvement in insomnia symptoms of participants was also shown by daily sleep diaries, with eight out of 17 (47%) showing a moderate or large treatment effect on frequency of night waking, 14 out of 17 (82%) showing a moderate or large treatment effect on sleep efficiency, and 10 out of 17 (59%) showing a moderate or large treatment effect on total sleep time. Interestingly, in terms of subjective sleep quality, just three out of 17 (18%) participants showed a moderate to large treatment effect. Additionally, just two out of 17 (12%) participants showed a moderate to large treatment effect for sleep onset latency, however only five participants presented with a problem in sleep onset latency to begin with. Therefore, greatest improvements were observed for the sleep efficiency and total sleep time variable measures, which is consistent with the findings of Lothian and colleagues (Lothian et al., 2016).

Additionally, a significant placebo effect was seen; however, greater reduction of severity of insomnia symptoms and greater improvement in sleep aspects measured by the CSD-M were observed during the micronutrient phase, thus supporting the hypothesis that the

micronutrient intervention had an effect additional to any placebo on primary measures of insomnia. This is evidenced as the overall group mean insomnia severity rating dropped from 21.29 at mean placebo to 15.71 at the end of treatment with a statistically reliable medium effect size (Cohen's  $d_{av} = -0.66$ , CLES = 78%), with 12 out of 17 participants experiencing a clinically significant reduction at end of treatment compared to placebo as shown by the modified Brinley plots. Additionally, the positive effect was also shown by the CSD-M sleep diary data, as the mean PEM for none of the sleep variables reached even a moderate effect size during placebo; and all mean PEM scores were higher in the micronutrient phase compared to placebo (see Tables 5 and 6). Thus, there was clearly an additional positive effect of the micronutrients. However, due to the short lengths of placebo phases, it is possible that the placebo did not have a sufficient amount of time to produce a maximum effect.

Short sleep duration is known to elevate levels of pro-inflammatory biomarkers (e.g., TNF- $\alpha$ , IL-1, IL-6) (Motivala, 2011; Vgontzas et al., 2003), and as aforementioned, previous research has found individuals with insomnia exhibit elevated levels of these biomarkers (Motivala, 2011; Vgontzas et al., 2003). The current study showed the greatest increase in total sleep time and sleep efficiency after micronutrient supplementation. It is plausible that the micronutrients reduced the levels of these pro-inflammatory biomarkers thus increasing total sleep time and sleep efficiency. However, as these biomarkers were not measured in the present research, this theory cannot be confirmed and thus needs further exploration.

The overall finding that the majority of participants reported significant reduction in insomnia on two or more aspects of sleep measured by the CSD-M, and reliable and clinically significant decrease in insomnia severity supports the findings of Lothian and colleagues (Lothian et al., 2016). This finding is strengthened in the current study as the results show the micronutrient intervention had an effect that was additional to any placebo effect, which is consistent with previous research investigating the same broad-spectrum micronutrient formula showing greater improvement in psychological functioning in adults compared to placebo

control (Rucklidge et al., 2014b) as well as against single/lower dose nutrients (Rucklidge et al., 2012). Additionally, the visual analyses of the multiple-baseline times series data show consistency whereby the positive effects of the micronutrients were replicated across a variety of measures, intervention phases and participants. This confirms that the changes were due to the micronutrient intervention, and that it is improbable that the results are due to natural improvements over time or regression to the mean. This replication of Lothian and colleagues (Lothian et al., 2016) research provides further evidence that broad-spectrum micronutrients are useful for the reduction of insomnia symptoms, and contributes to the idea that a range of micronutrients may be more beneficial and reliable for treating chronic insomnia than single nutrients alone. Thus, this challenges the typical experimental method of only providing single nutrients to evoke insomnia and other psychological symptom change (Rucklidge & Kaplan, 2013). The findings of the present research are also consistent with numerous other studies demonstrating the benefits broad-spectrum micronutrient formulas have on mental health (Kaplan, Rucklidge, Romijn, & McLeod, 2015; Rucklidge & Kaplan, 2013).

The effect of the intervention can also be demonstrated in a qualitative way through comments by participants. Six participants commented that they were “not waking up as much during the night”; and seven commented they “get back to sleep quickly” if they did awake; and eight commented “I have more energy” and “feel more refreshed”. Additionally, three participants noted that they “feel more clam”, especially given the busyness of the end of the school year.

Cognitive and physiological hyperarousal are often associated with insomnia. A stressful emotional climate (e.g., a classroom with many children with behaviour problems) is likely to enhance the risk of hyperarousal through worry, anxiety and rumination, which can thus contribute to disruption of neurobiologic systems that modulate stress-response and sleep-wake regulation (Palagini et al., 2014). Therefore, it is reasonable to assume that cortical and physiological hyperarousal (i.e., disrupted sleep physiology) may be reduced and emotional

processing abilities enhanced due to a constant supply of an abundance of micronutrients, which help to support all the biochemical processes necessary for optimal brain function (Kaplan et al., 2015b). Consistent with this, and as will be discussed below, in the current study, out of the MBI-ES measures, the micronutrients had the greatest effect on reported emotional exhaustion levels.

Sleep diary data provided by the current sample was often variable, which is in contrast to the findings of Lothian and colleagues (Lothian et al., 2016). Some variability observed was associated with factors related to the teaching profession (e.g., staying up late writing reports). For example, whilst all teachers would have been report writing during the micronutrient phase, staying up late was noted in sleep diaries by participant P2 in weeks six and seven; by participant P5 in week seven; by participant P6 in weeks three four and five; and in person by participant P4. Additionally, participant P6 noted that they spent a considerable amount of time organising a school hangi during week 2; and participant P5 spent time organising a class presentation for an assembly in week one. Such a pattern is consistent with the idea that teaching is a stressful occupation with a high workload (Kyriacous, 2001). Other factors contributing to disrupted sleep included personal and family sickness throughout the intervention period, and social events over the Christmas holiday period at the end of the micronutrient phase. For example, participants P1, P2, P3, P5, P9, P10, P14 and P16 noted over varying days and weeks of the micronutrient phase that they were experiencing personal sickness; participants P3, P13, and P16 noted in weeks 3 and 5 respectively that sleep was disrupted due to family sickness; and participants P2, P5, P6, P7, P11, P13, and P17 noted that they attended social events during the final week that disrupted their normal routine. However, although sleep patterns varied from night to night, the micronutrient intervention often reduced variability, which in itself may be beneficial.

The times-series graphs show that for some participants sleep was disrupted during the last week of the intervention (i.e., decreases seen in sleep efficiency and total sleep time, and increases in number of night wakings). Additionally, the treatment effect for all groups



combined is slightly less at treatment end ( $d_{av} = -1.37$ ) compared to week 4 of treatment ( $d_{av} = -1.44$ ), albeit these effect sizes are still large and statistically reliable. Therefore, one consideration when interpreting the findings is that although teachers were not teaching in the classroom at the end of treatment, the micronutrient phase of the intervention was completed the week of Christmas, and the external factors around Christmas, a known stressful, busy and active social time, may have impacted results.

**Depression, anxiety and stress symptoms.** In terms of wellbeing measures, the hypothesis that the micronutrient intervention would be associated with improvements in stress, anxiety and mood symptoms if relevant, relative to placebo was not supported. In terms of anxiety, end of treatment relative to initial baseline scores indicates that reduction in anxiety was statistically reliable (i.e., the mean change in scores were statistically significantly different from zero) with a medium-large effect size ( $d_{av} = -0.73$ , CLES = 82%). However, decrease in anxiety from initial baseline to mean placebo was statistically reliable with a small effect size ( $d_{av} = -0.36$ , CLES = 68%); and although a small reduction in anxiety from mean placebo to end of treatment was observed ( $d_{av} = -0.34$ , CLES = 67%), the mean change cannot be interpreted as reliable (i.e., the mean change in scores were not statistically significantly different from zero). Additionally, any clinically or statistically significant reduction in anxiety is unlikely because anxiety levels were not generally clinically elevated in baseline and therefore there is a floor effect. Consequently, not only is any further effect of the micronutrients compared to placebo hard to detect, it is also hard to detect anything other than deterioration because of the floor effect.

In terms of depression and stress, the results for changes in depression and stress levels were not statistically reliable at end of treatment relative to initial baseline, despite the mean reductions being in the desired clinical direction. Additionally, mean reductions in stress at both week four and end of treatment relative to mean placebo were not statistically reliable, as well as mean reduction in depression at week four. The end of treatment relative to mean placebo saw a

slight increase in depression scores at end of treatment, albeit this increase was not statistically significant. The scores of two participants increased to the clinical cut-off line, perhaps due to the time of the year at end of treatment assessment (as discussed above). Note that one participant was experiencing difficult family circumstances at the time of the end of treatment assessment. Lack of clinically and statistically significant reduction in depression and stress scores is again unlikely as few participants were in the clinical range for stress and depression at initial baseline, thus reflecting a floor effect. This general floor effect again makes anything other than deterioration and any additional effect of the micronutrients compared to placebo hard to detect. Thus, micronutrient consumption was not associated with a significant reduction in stress and depression levels, and the hypothesis that the micronutrient intervention would have an effect additional to any placebo on wellbeing measures was not supported, but this conclusion has to be qualified by noting that levels were not generally clinically raised to begin with.

The finding that anxiety levels were not significantly reduced relative to placebo after micronutrient consumption is in contrast with previous research investigating the effect of broad-spectrum micronutrients on anxiety in adults after stressful life events (Kaplan, Rucklidge, Romijn, & Dolph, 2015; Rucklidge et al., 2012; Rucklidge et al., 2014; Rucklidge & Blampied, 2011); however, it is important to note that these studies did not use placebo control. Furthermore, reduction in stress in the current study was not reliable. Although sixteen out of seventeen participants' stress scores were below the clinical cut-off level, the lack of significant reduction in stress levels at end of treatment appears contrary to the findings of Lothian and colleagues (Lothian et al., 2016) and several other previous studies investigating the effect of broad-spectrum micronutrients on stress and anxiety (Rucklidge et al., 2012; Rucklidge et al., 2014; Rucklidge & Blampied, 2011). But again, this reflects a floor effect as few participants scored above the clinical cut-off at initial baseline. Additionally, the finding that the current study did not yield a significant reduction in depression levels is contrary to previous research using clinical samples of individuals with depression (Gatley & Kaplan, 2009; Rucklidge &

Harrison, 2010; Simmons, 2003), but is however, consistent with previous research using non-clinical samples for depression (Kaplan, Rucklidge, Romijn, & Dolph, 2015; Long & Benton, 2013).

The finding that the micronutrient intervention did not have an effect additional to any placebo on wellbeing measures is in contrast with the previous research mentioned above using placebo control (Rucklidge et al., 2014b), and single/lower dose nutrient comparisons (Rucklidge et al., 2012). This finding too, is also in contrast with previous research investigating multi-ingredient micronutrient formulas, which are not EMP+, against placebo (Carroll et al., 2000; Stough et al., 2011); however, comparisons are difficult due to the varying formulas and doses used.

There are several possible reasons for the lack of significant effect of micronutrients on stress, anxiety and depression levels in the current study. First, participants were selected for the study if they met criteria for insomnia, not for high anxiety, depression and stress scores. The current sample were a non-clinical sample with respect to depression, anxiety and stress, thus scores were low at initial baseline meaning there was not much room for any further reduction. It is noteworthy, however that depression scores, as well as stress and anxiety scores, did not significantly deteriorate over the course of the intervention.

The finding that reduction in stress scores was not reliable was unforeseen as this sample was selected due to their high-stress working environment. However, only two participants' scores were above the clinical cut-off at initial baseline. One explanation for low baseline scores is that baseline measures were taken in the second week of the school holidays in order that the intervention could begin in term 4 of the school year. Thus, teachers had not been in the stressful classroom environment for over a week preceding initial baseline assessment, potentially providing teachers with enough time to de-stress without other significant factors (e.g., Christmas), before the intervention began. However, as previously mentioned, stress is not the sole cause of insomnia. It is possible that worry, rumination and physiological hyperarousal

played a larger role in maintaining insomnia at the time baseline measures were assessed than stress. Another plausible explanation is the possibility that there was some inadequacy in the DASS-21 measure, which may not have been sensitive to stress in the current sample. A scale specifically measuring teacher occupational stress, such as the Teacher Stress Inventory (Fimian, 1984), may have been more sensitive and thus detect any change in stress.

**Burnout.** Burnout was measured in this study because it has been widely investigated as a deleterious state experienced by teachers (and other employees) who have worked under stressful conditions for periods of time. The hypothesis that the micronutrient intervention would be associated with improvements in the burnout dimensions of emotional exhaustion (EE) and depersonalization (DP) was partially supported in that the group mean ratings for the EE subscale of the MBI-ES dropped from 31.59 at baseline to 22.18 at treatment end with a statistically reliable and large effect size (Cohen's  $d_{av} = -1.08$ , CLES = 93%). A clinically significant reduction was observed in 11 out of 17 participants in the EE subscale. No clinically or statistically significant reduction was observed in the DP subscale because DP levels were not generally clinically elevated in baseline and therefore there is a floor effect; consequently, it is hard to detect anything other than deterioration.

Although previous micronutrient research has not specifically focused on EE, the finding that micronutrient consumption is associated with improvements in EE is consistent with previous research in the sense that broad-spectrum micronutrients have been associated with improvements in sleep, anxiety and stress (Lothian et al., 2016; Rucklidge et al., 2012). This is because, as EE refers to a depletion of emotional resources and shortage of energy (Maslach, Schaufeli, & Leiter, 2001), it is not surprising that improvements in sleep are likely to positively impact EE. Micronutrient supplementation may have also provided participants with a renewed capacity to process emotional states effectively as a result of renewed energy from sleeping efficiently.

Furthermore, as EE is likely to place individuals under cognitive strain, the findings of the current study are consistent with previous research finding improvements in cognitive functioning and mental fatigue after micronutrient consumption (Haskell et al., 2010). The finding that Christchurch teachers reported significant improvement in EE is both positive and encouraging as being able to function optimally is vital to not only their teaching role, but also to cope effectively with the extra stressors children in their classrooms bring (e.g., behaviour problems, difficulty concentrating). Such findings also confirm the idea that better sleep leads to improvements in daytime functioning and vice versa.

An explanation for the lack of significant decrease in DP in the current study is that scores were not high at initial baseline. First, this may be due to the fact that participants were not teaching in the classroom at this time. Second, EE is a probable precursor to DP (Maslach et al., 2001), thus, the micronutrients may have protected against the onset of DP occurring due to its successful reduction of EE. Third, and perhaps the more likely scenario, low scores observed may reflect the characteristics of the particular study sample used. Thus, although participants were fatigued, they did not exhibit negative or indifferent attitudes toward their students or psychological detachment from their work (Maslach et al., 1996). It is also noteworthy that scores did not worsen over the course of the intervention indicating that micronutrient supplementation may have supported maintenance of low scores.

**Follow-up.** The hypothesis that improvements would be maintained over the follow-up period if participants remained on the micronutrient formula; and that improvements would be maintained at a lower level for participants who discontinued was partially supported. All 17 participants provided follow-up data. In the overall group, no further reduction in severity of insomnia was seen from the end of the intervention to the 3-month follow-up, and the majority of participants displayed some moderate return back toward initial baseline. Statistically significant improvements in insomnia symptoms over the follow-up period relative to initial baseline were maintained, thus indicating an enduring effect of the micronutrients even in those

that discontinued use after the intervention; however, although mean reduction in insomnia severity observed at follow-up relative to mean placebo was in the desired clinical direction, this difference was not statistically reliable. Thus, although 10 participants demonstrate clinically significant reduction in insomnia levels at follow up relative to placebo (i.e., they were below the clinical cut-off), there was no statistically significant additional enduring effect of the micronutrients relative to the placebo effect. As such, although improvements in insomnia severity were maintained at follow up relative to initial baseline, reduction in insomnia severity was not statistically significantly reduced at follow up in comparison to the placebo effect observed.

Of the four participants who continued taking EMP+ after the intervention, treatment benefits were maintained and large and medium-large effects were shown at follow-up relative to initial baseline ( $d_{av} = -0.90$ , CLES = 88%) and mean placebo ( $d_{av} = -0.64$ , CLES = 69%) respectively. However, a slight increase in insomnia severity is seen at follow-up relative to end of treatment, as mean insomnia severity rating scores increased from 18.5 at treatment end to 19.75 at follow-up ( $d_{av} = 0.07$ , CLES = 54%). Although this is contrary to the hypothesis, it is noteworthy that one of these 4 participants experienced a death in the family, which is likely to have significantly impacted this finding, as such an event is upsetting and stressful, thus negatively impacting sleep. When this participant is taken out of the analysis, treatment continued to confer benefit as mean insomnia severity scores dropped from 13.67 at treatment end to 10 at follow-up, with a small effect size ( $d_{av} = -0.35$ , CLES = 63%), and dropped from 30.17 at mean placebo to 10 at follow-up, with a very large effect size ( $d_{av} = -6.14$ , CLES = 100%), indicating both continued reduction in severity of insomnia for these three participants and an additional enduring effect of the micronutrients relative to the placebo effect. However, these findings should be interpreted with caution as the 95% CI on  $d$  was not computable (because the data violated the requirements for iterative computation built into the software), therefore it cannot be determined whether this change was statistically reliable.

Considering depression, anxiety and stress scores, no further improvement was seen at the 3-month follow-up, with the majority of participants displaying some return back toward initial baseline. Of the four participants that continued, no further improvement was seen in total DASS-21 scores at follow-up compared to initial baseline, as mean total DASS-21 scores increased from 10 at treatment end to 12.25 at follow-up, with a small effect size ( $d_{av} = 0.22$ , CLES = 54%). Again, this is largely due to participant P6 experiencing very difficult family circumstances. When this participant is taken out of the analysis, treatment continues to confer benefit as mean total DASS-21 scores dropped from 8.67 at treatment end to 6 at follow-up, with a medium effect size ( $d_{av} = -0.50$ , CLES = 71%), indicating continued reduction in total DASS-21 scores. Mean scores of these three participants decreased from 16 at initial baseline to 8.89 at mean placebo, with a large effect size ( $d_{av} = -1.01$ , CLES = 82%), thus indicating a placebo effect. Furthermore, no further reduction in DASS-21 scores was seen in these participants at end of treatment relative to mean placebo, as mean scores decreased only from 8.89 at mean placebo to 8.67 at treatment end ( $d_{av} = -0.04$ , CLES = 52%); which is consistent with the floor effect observed in the overall sample. Despite this, a reduction in total DASS-21 scores continued to be observed relative to placebo as mean total DASS-21 scores dropped from 8.89 at mean placebo to 6 at follow-up, with a large effect size ( $d_{av} = -0.90$ , CLES = 88%), thus indicating that there may have been an additional enduring effect of the micronutrients in those that continued at follow-up relative to the placebo effect. However, again, these findings should be interpreted with caution as the 95% CI on  $d$  was not computable it cannot be determined whether this change was statistically reliable.

The finding that those who continued taking EMP+ reported greater maintained improvements in insomnia and daily functioning at follow-up compared to those who chose to discontinue is consistent with previous research into other psychiatric diagnoses such as anxiety and ADHD (Rucklidge et al., 2014; Rucklidge et al., 2014b). Together these findings indicate that the benefits of micronutrients produce greater positive treatment effect in those that

continue, and diminish in those that do not. One participant in the current study (P10) who responded remarkably to the micronutrients during the intervention reported switching back to medication (zopiclone) and the end of the trial due to the cost of the micronutrients. At follow-up, this participant reported an increase in severity of insomnia from a PIRS-20 score of 3 at the end of the intervention to 37 at follow-up. Total DASS-21 scores also increased from 3 and treatment end to 17 at follow-up. Thus, insomnia severity increased and overall wellbeing decreased upon discontinuation of the micronutrients for this participant despite their resumption of medication. This is in line with Rucklidge and colleagues (Rucklidge et al., 2014; Rucklidge et al., 2014b), who found in their follow-up studies that participants who switched to medications from micronutrients experienced a worsening in symptoms. This is also consistent with research demonstrating the negative outcomes of long-term medication use in both insomnia (Krakow, Ulibarri, & Romero, 2010) and other psychiatric diagnoses such as depression, anxiety and ADHD (Advokat, 2010; Offidani, Fava, Tomba, & Baldessarini, 2013). Thus, the findings that consumption of micronutrients led to continued improvement in symptoms over time suggest that micronutrient supplementation for chronic insomnia and other psychiatric difficulties is a viable treatment option in the long term.

Reasons given by participants for continuing the micronutrients included improved sleep, mental health and improved physical health conditions including irritable bowel syndrome (Nicholson et al., 2012) and reduction in menopause symptoms (e.g., night-sweats and hot flushes). For example, one participant commented that “I feel better and I sleep better”, another “my sleep has improved and irritable bowel is gone!” and another “the micronutrients helped me get back to sleep and my night sweats and hot flushes are way better”. As discussed in the introduction, there is a strong relationship between gut dysbiosis, inflammation and many chronic disorders. Both psychological and physiological stress (e.g., disturbed sleep physiology) negatively alter the balance of good and bad gut bacteria, and reduction in beneficial bacteria can evoke inflammatory responses and can thus be an underlying cause of inflammatory diseases



such as IBS (Berk et al., 2013). Reported reduction in IBS in the current study is consistent with the idea that insomnia and other psychiatric diagnoses are associated with gut dysbiosis and elevated levels of proinflammatory cytokines, which can in turn be corrected through micronutrient supplementation (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Additionally, microbiome and hormonal changes occur as individual's age and can be negatively altered during menopause for women (Zapata & Quagliarello, 2015). Reported reduction in menopause symptoms in the current study may thus indicate that micronutrients could correct these imbalances, which in turn may keep menopausal symptoms at bay. Though, it is important to remember these theories cannot be confirmed in the present research as proinflammatory biomarkers were not measured. However, the link between micronutrient supplementation and premenstrual syndrome is currently being investigated (Retallick-Brown, Rucklidge, & Blampied, 2016), which may provide further information on the association between hormonal changes and micronutrient supplementation.

Reasons given by participants for not continuing to take the micronutrients included cost, procrastination, life stress, that no difference in sleep or positive effect was noticed during the intervention and simply that they did not suit. For example, one participant commented, "I did not find they made much difference"; another "I didn't feel certain that they were improving the quality of my sleep. Interestingly, having completed this survey, I realise the quality of my sleep may be where it was pre-intervention so the nutrients probably made some difference"; and another "wanted to try without them and see if there was a difference or not". Importantly, side effects or feasibility of taking the pills were not identified as a reason to discontinue the micronutrients.

**Side effects.** The final hypothesis that the micronutrient intervention would not be associated with significant side effects, and if present, these would be minor and transitory, was supported. Side effects were reported by a total of 11 participants: 10 participants during the micronutrient phase. Of these, four participants also reported side effects during the placebo

phase. One participant reported headaches and gastrointestinal disturbances during the placebo phase only. Six participants never reported any side effects. The majority of adverse side effects experienced by participants were mild (e.g., headaches, gastrointestinal disturbance), with one participant experiencing side effects at a moderate level (e.g., headaches). Side effects experienced were transitory and able to be remedied through increased water and food intake. No participant withdrew because of adverse side effects. Furthermore, side effects reported during placebo phases (e.g., headaches and gastrointestinal disturbance) by five participants may have been due to the expectation that side effects will occur, thus meaning these individuals may have been more likely to attribute ambiguous or pre-existing sensations to pill taking. This may also have been true for some participants during the micronutrient phase, as participants commonly reported that they were not sure if the side effects they were currently experiencing were due the micronutrients or not; however, this theory cannot be confirmed. Additionally, four out of the five participants reporting side effects during placebo reported that they were not used to taking any sort of pills, thus it may have been that reported side effects were due to the body adapting to pill taking with the placebo formula.

The finding that the current study was not associated with any significant adverse side-effects or safety concerns is consistent with previous research (Lothian et al., 2016; Rucklidge et al., 2012; Rucklidge et al., 2014a; J. S. A. Simpson et al., 2011). The current study thus adds to the existing literature demonstrating the positive safety and tolerability findings of EMP+.

## **4.2 Research Strengths**

One strength of this study was the strengthening of the multiple-baseline design with placebo control. Use of a placebo meant that the first two weeks of the intervention was double-blinded and from thereafter single-blinded. This allowed for detection of the portion of the overall treatment effect that was attributable to the micronutrients. It also allowed for any expectancy effects to be controlled for, and multiple replications of treatment benefit could be seen across participants throughout the micronutrient phase. This design also allowed for

baseline stability of symptoms to be evaluated and for symptoms to repeatedly be assessed.

Taken together, this demonstrates that positive treatment effects found in the current study are beyond that of regression to the mean effects or people improving naturally over time. The design also allowed for all participants to receive the active intervention, and for between and within-group comparisons of the intervention to be made. This has ethical advantages over conventional designs, which consign some participants to control conditions and denying them access to benefits of the active treatment.

Retention rate in the current study was high with no dropouts, compliance was very good, and four participants chose to continue taking the micronutrients, indicating that micronutrient supplementation is a feasible and viable treatment option. One factor that this may be due to is that throughout the intervention, the researcher often met with participants at a place of their convenience, and not at the University. This meant participants did not have to leave their place of work or home and travel a fair distance to the university, thus keeping disruption to their lives to a minimum and making it convenient for them to remain in the study. Additionally, there was a low level of missing data. It is likely that use of online surveys helped with this, and use of a paper and pen sleep diary made it simple to fill out and easily accessible to participants.

A further strength is that because this study was occupationally focused and only recruited teachers, this controlled for any differences that might have been introduced due to individuals being in different jobs or having different sources of daily stressors. Another strength is that this trial was prospectively registered on the Australia New Zealand Clinical Trials Registry, which ensured that key methodological aspects of the study such as the primary outcome measures were not changed after the study was registered, ensuring reporting of outcomes was transparent (Bradley, Rucklidge, & Mulder, 2016).

#### **4.3 Limitations**

There were several limitations of the present study that must be acknowledged. First, one major limitation is that the DASS-21 measure used at screening and over the course of the

intervention may not have been the appropriate measure to use to detect teacher stress, anxiety and depression. Alternate measures of anxiety and depression, and a scale specifically designed to measure teacher occupational stress, such as the Teacher Stress Inventory (Fimian, 1984), may have been more sensitive. Second, another major limitation is the timing that measures were assessed. All baseline measures were assessed in the second week of the school holidays. This is likely to have impacted the findings as participants were not in their normal daily routines and were not currently teaching in the classroom. Thus, it is possible that participants were less stressed and more relaxed at the time of baseline assessment. Furthermore, end of treatment measures were assessed during the week of Christmas. This is again likely to affect the current findings due to Christmas being a stressful and busy time of year, with many participants attending numerous social events and being out of their normal daily routine, which in turn affects sleeping patterns.

Influences contributing to the positive findings may include improved sleep patterns and sleep hygiene through use of completing a daily sleep diary. Some participants commented that they learnt that they did not have healthy sleeping habits and patterns, and it is thus plausible that some participants may have tried to rectify this. However, previous research shows that there is an inadequate amount of empirical evidence to suggest sleep hygiene education is an effective treatment on its own (Stepanski & Wyatt, 2003), with one study showing that it is ineffective as a stand-alone treatment (Schocket, Bertelson, & Lacks, 1988). Additionally, daily routines may have improved through the need to eat regularly and drink plenty of water with the pills. However, as sleep habits, sleep hygiene, and nutritional intake were not assessed, the degree to which these factors influenced the findings cannot be verified.

Another limitation of the present research is that as nutritional intake and pro-inflammatory and oxidative stress biomarkers were not assessed, possible mechanisms of action for insomnia could not be identified. However, it is important to note that collection of this data was beyond the practical scope of this study.

Researcher contact and therapeutic input are often involved in research trials such as these, and may have contributed to the improvements seen in the current study. However, therapeutic input and contact is unlikely to explain the magnitude of positive change observed in participants throughout the intervention as the study was designed to keep researcher contact to a minimum, meetings were kept short (generally less than 30 minutes), sleep diaries were completed at home, and the remaining assessments completed online. Meetings were arranged to discuss how participation was going and to check for any side effects and compliance. Participants were not provided with psychological strategies to cope with their insomnia.

Spontaneous remission of symptoms should also be considered; however, because a positive effect was experienced by the majority of participants experiencing chronic insomnia, spontaneous remission being responsible for the treatment effect observed is improbable. Additionally, the pattern of change seen i.e., stability of baselines and greatest improvements observed in the micronutrient phase, makes treatment effects observed due to spontaneous remission unlikely.

Although a placebo was used to help control for any expectancy effects, experimenter bias should be considered as a possible contributing factor to improvements seen. While the first two weeks of pill taking were double-blind, meaning neither the participant nor researcher knew if they were in active intervention, after two-weeks the researcher knew that all participants were receiving the micronutrients. This meant that the study then became single-blinded and experimenter bias may have occurred during later meetings with the participants. However, again this is unlikely as meetings were kept to a minimum, a multiple-baseline design was used and measures completed at home or online. Furthermore, treatment benefits were small initially and increased the longer participants had been taking the micronutrients.

Further limitations include the small sample size. However, the fact that significant improvement in insomnia was found in both the current study and that of Lothian and colleagues (Lothian et al., 2016) who had a small sample size of 14 participants, suggests that the effect of

micronutrients on insomnia could be a considerable one. Second, generalizability (i.e., the external validity) of the results are limited as the current study was occupationally focused and consisted of teachers in Christchurch working in a city affected by earthquakes and in turn experiencing multiple stressors. Thus, generalizing to teachers working in a city not affected by earthquakes and to other occupations who experience different sources of stress is difficult. Despite this, it is important to remember that the current findings of the effect of micronutrient supplementation on insomnia replicate the findings of Lothian and colleagues (Lothian et al., 2016) whose sample was a general adult population. However, in both the current study and that of Lothian and colleagues (Lothian et al., 2016) the majority of the samples consisted of women, therefore, generalizability to men is difficult to determine. It is important to remember however, that insomnia affects more women than men (Morin & Jarrin, 2013) and could explain why both study samples were predominantly female. Additionally, teachers also tend to be predominantly female, which is therefore a further explanation as to why the current study sample contained fewer men.

#### **4.4 Implications**

The current research has a number of implications for future research and practice. First, the present research contributes to the limited research on the effect of broad-spectrum micronutrients and chronic insomnia. The current body of research provides mixed results across various individual vitamin and mineral treatments for insomnia, as well as lower dose multi-nutrient treatments. The findings of the present research indicate that there needs to be a focus on providing individuals with a broad range of micronutrients at higher doses in order to see a significant improvement in chronic insomnia. This is consistent with the idea that physiological functioning is enhanced when vitamins and minerals are given in combination as they affect both the absorption and effectiveness of one another. Thus, the present study offers further evidence that use of broad-spectrum micronutrients for the treatment of chronic insomnia has potential as a viable treatment option and is worthy of further exploration; and that it is important for

clinicians to be open to and recommend alternative treatment options for chronic insomnia, such as EMP+. This would ensure teachers and individuals with chronic insomnia are provided with an additional treatment option, and can make an informed decision about which treatment may suit them best.

Second, the potential metabolic mechanisms specifically associated with insomnia are unable to be identified in the current study, as the aim was to determine any intervention effect of micronutrient supplementation. However, present findings suggest metabolic mechanisms discussed in the introduction section are important to take into consideration with the effects of EMP+ on chronic insomnia. This theory undoubtedly deserves further exploration. Thus, the present research provides a foundation for further investigation into the application of broad-spectrum micronutrient supplementation for chronic insomnia in clinical populations.

#### **4.5 Future Research**

As mental health needs continue to rise in Christchurch post-disaster (McLennan, 2016), many people seek alternative treatment for insomnia as well as other psychiatric disorders due to the limited availability of public services, cost of therapeutic intervention, and lack of efficacy, long-term risks and side effects associated with pharmacological treatment (Rucklidge & Kaplan, 2013). Thus, alternative treatments for these difficulties need to be explored. The objective of the current study was to determine whether micronutrients would be one such alternative for insomnia and work-related stress. Because possible mechanisms of action of micronutrients associated with insomnia were not measured in the present research, nutritional intake and metabolic levels of vitamins and minerals were not assessed. Future research however, should endeavour to incorporate such measures, which could inform whether the dietary intake of individuals with insomnia working in a stressful environment is inadequate or whether nutritional needs increase in response to the increased physiological and external stress, or both.

Furthermore, as the findings suggest there may be a likely link between the gut, oxidative stress, inflammation and mitochondrial dysfunction and insomnia, especially as one participant who experienced reduction in insomnia also experienced reported reduction of IBS; and given the association between elevated pro-inflammatory biomarkers, gut health and insomnia (Motivala, 2011; Vgontzas et al., 2003), future research should endeavour to collect information on levels of pro-inflammatory biomarkers (e.g., TNF-alpha, IL-6, IL-1, CRP) and oxidative stress biomarkers (e.g., SOD). This would allow determination of the effect of micronutrients on the inflammatory nature of chronic insomnia. Faecal sampling would be beneficial in future research as a way to further assess micronutrient outcome on insomnia and to determine whether micronutrients can increase the diversity of bacteria in the gut, which in turn increases gut health, thus enhancing micronutrient absorption (Kaplan, Rucklidge, Romijn, & McLeod, 2015). Research clarifying the specific mechanisms of action of micronutrients on insomnia would also be beneficial, because as previously mentioned in the Introduction, currently the mechanisms of action specifically related to insomnia have not been identified (Berk et al., 2013). Such methodology would add to the growing body of literature on the role of micronutrients in mental health, and would add to the knowledge of the etiology, maintenance and treatment of chronic insomnia.

The present research could be extended by employing a randomised controlled trial design incorporating a placebo. Such research would add to evidence of the micronutrients' effectiveness (or otherwise), and would further minimise any bias and unknown confounding variables through random allocation to active and placebo control conditions. Additionally, numerous treatment variants (e.g., length of trial, dose, formula) and participant (e.g., gender, age) aspects should be systematically replicated in future research to determine generality of the treatment effect over diverse cases and treatment settings. This can most efficiently be done by use of systematic replications within single-case research (Blampied, 2013). In the current study, some participants noted at the end of the intervention (after about 8 weeks receiving



micronutrients) that they started to notice an improvement in sleep (i.e., a reduction in insomnia symptoms). This suggests that longer trials may produce greater reduction in insomnia in participants. Also, it is reasonable to assume that optimal doses for therapeutic benefits vary between individuals; it may be that a higher dose than that used in the present study would be of greater benefit to some individuals while some may be able to retain benefits at a lower dose. Therefore, it is of great importance that varying doses and longer intervention phases are explored. Furthermore, given that the samples in both the current study and that of Lothian and colleagues (Lothian et al., 2016) were predominantly female, future research should endeavour to obtain gender balance or specifically investigate males in subsequent trials in order to increase generality of findings. Also, future research should employ appropriate occupationally focused measures, as well as anxiety and depression measures, to detect for any change in stress, anxiety and depression. Additionally, it is desirable for future research to conduct comparisons with psychological treatments for insomnia such as CBT-I (Morin, 2004; Siebern, Suh & Nowakowski, 2012), as it may be found that symptom reduction and the effectiveness of psychological treatment is enhanced when micronutrients are used in conjunction.

Given the positive findings of the current study and that of Lothian and colleagues (Lothian et al., 2016), it is plausible that micronutrient supplementation may also be useful for the prevention of insomnia. In the present research, teachers were teaching in the classroom for the majority of the intervention. Thus, for most of the teachers insomnia symptoms reduced whilst teaching in a stressful working environment. These findings suggest that micronutrients may protect against the development of insomnia. Because of the earthquakes, Christchurch teachers are facing different challenges than those around the rest of New Zealand, therefore, supplementing with micronutrients before mental health problems arise, or in anticipation of or early in exposure to stressful events, may prove invaluable, and is something that future research should explore.

Long-term efficacy and safety of micronutrient use over several years has not yet been ascertained (Rucklidge & Kaplan, 2013), therefore, further research should establish long-term outcomes, for the most part on brain development. However, preliminary reports of continued use without adverse effects (J. S. A. Simpson et al., 2011) provide positive support for long-term use. Additionally, it would be beneficial for future research to systematically determine, once reduction of symptoms has been attained, whether the dose can be decreased to a maintenance level.

#### **4.6 Conclusion**

The aim of the current study was to investigate the effect of a broad-spectrum micronutrient formula taken over an over an 8-10 week period when compared with placebo for the treatment of chronic insomnia in teachers in Christchurch. The findings show that broad-spectrum micronutrient supplementation is beneficial for the treatment of chronic insomnia in teachers working in a stressful environment, as well as for the reduction of emotional exhaustion in Christchurch teachers. It is possible that the lack of effect of micronutrients on stress, anxiety and depression is due to scores not being generally clinically raised in the sample to begin with; as well as potential inaccuracy in the measure. The positive effect of micronutrients on insomnia confirm the findings of Lothian and colleagues (Lothian et al., 2016), and provide further support to the current body of research demonstrating that improvements in a range of psychiatric symptoms and overall functioning occur after supplementation with a broad-spectrum of micronutrients. These findings indicate that broad-spectrum micronutrients are a viable treatment option for Christchurch teachers experiencing chronic insomnia. In turn, teachers who are functioning optimally will be able to provide the best education and care that they can for their students, including those that continue to display problem behaviours as a result of the earthquakes. While future research is needed to both replicate and strengthen the findings and determine the specific biological mechanisms associated with insomnia and the

effect micronutrients have on them, the present research establishes a solid foundation upon which such research can build.

## 5. References

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## 6. Appendices

### Appendix A: Ingredient List of EPowerplus

#### EMPowerPlus Advanced Supplement Facts

Amount Per Serving (2 capsules)*		% Daily Value
Vitamin A (as retinyl palmitate)	768 IU	16
Vitamin C (as ascorbic acid)	80 mg	134
Vitamin D (as cholecalciferol)	192 IU	48
Vitamin E (as d-alpha tocopheryl succinate)	48 IU	160
Thiamin (as thiamin mononitrate)	2.4 mg	160
Riboflavin	1.8 mg	106
Niacin (as niacinamide)	12 mg	60
Vitamin B6 (as pyridoxine hydrochloride)	4.8 mg	240
Folic acid	342 mcg	48
Vitamin B12 (as methylcobalamin)	120 mcg	2000
Biotin	144 mcg	48
Pantothenic acid (as calcium pantothenate)	2.9 mg	29
Calcium (as chelate)	176 mg	18
Iron (as chelate)	1.9 mg	10
Phosphorus (as chelate)	112 mg	11
Iodine (from Pacific kelp)	27.2 mcg	18
Magnesium (as chelate)	80 mg	20
Zinc (as chelate)	6.4 mg	43
Selenium (as chelate)	26.5 mcg	38
Copper (as chelate)	1 mg	48
Manganese (as chelate)	1.3 mg	65
Chromium (as chelate)	84 mcg	70
Molybdenum (as chelate)	20 mcg	27
Potassium (as chelate)	32 mg	1

Propriety blend: Choline bitartrate, DL-phenylalanine, citrus Bioflavonoids, Inositol, L-Glutamine, L-Methionine, Grape seed extract, Ginkgo biloba leaf extract, ermanium sesquioxide, Boron (as chelate), Vanadium (as chelate), Nickel (as chelate).

Other ingredients: capsule shell (gelatin, titanium dioxide) microcrystalline cellulose, glycine, citric acid, magnesium stearate, silicon dioxide, mineral wax

\*Amount per serving on this list is for 2 capsules. Participants need to be aware that they are taking 4x this amount (8 capsules per day).

## Appendix B: Information sheet and FAQ sheet

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**Date:** 10/05/16



### **Investigating the Effect of Micronutrients on Insomnia in Teachers: A Multiple-Baseline Design**

#### **Information Sheet for Teachers Experiencing Insomnia**

**Principal Investigator:** Alison Carley ([Alison.carley@pg.canterbury.ac.nz](mailto:Alison.carley@pg.canterbury.ac.nz))

**Other Investigators:** Professor Neville Blampied ([Neville.blampied@canterbury.ac.nz](mailto:Neville.blampied@canterbury.ac.nz)), Professor Julia Rucklidge ([Julia.rucklidge@canterbury.ac.nz](mailto:Julia.rucklidge@canterbury.ac.nz)), Associate Professor Kathleen Liberty ([Kathleen.liberty@canterbury.ac.nz](mailto:Kathleen.liberty@canterbury.ac.nz))

#### **What is the purpose of the study?**

This study is investigating the effects of a micronutrient formula (vitamins and minerals) on insomnia in teachers. The supplement we are studying is called EMPowerplus (EMP+) and the aim of the study is to determine whether this micronutrient formula can impact on symptoms of insomnia in teachers working in earthquake affected schools.

#### **What would I have to do?**

If you volunteer to participate in the study, before it begins you will be screened for eligibility first through an online questionnaire (approximately 30 minutes) and secondly through an interview with the researcher either at the University of Canterbury or a place of convenience for you, where written informed consent will be obtained and inclusion criteria will be reviewed (approximately 1 hour).

This study has two phases, and if you agree to take part, you will be asked to do the following:

- Phase one: You will complete the online baseline questionnaire on sleep quality and associated psychological measures. These will take 5-10 minutes each to fill out. After the first initial meeting, you will be asked to complete a daily sleep diary to be filled out every morning for 7 days, that asks questions about the previous night's sleep, in order to obtain baseline measures of sleep. This will take 5 – 10 minutes each day.
- Phase two: After the 7 days of baseline you will complete the questionnaires online again. Phase two is where the placebo and micronutrient phase



begins, where you will have up to 11 weeks of taking capsules (non-active placebo and active micronutrient). You will take 8 capsules daily, as two doses of four capsules twice a day. During this phase, you will continue to monitor your sleep daily using the sleep diary. You will be asked to meet with the researcher once a month or as necessary to assist with compliance and or resolve any side effects. You will be asked to complete online questionnaires at weeks 2, 3, 4, and 8. These will take 5 – 10 minutes to complete. At the end of the phase you will be asked to fill out again the questionnaires on sleep and associated psychological measures.

- Approximately three months after the trial is over you will be asked to fill out two online questionnaires for a final time on your insomnia symptoms and associated psychological measures.

### ***What are the risks?***

This type of supplement has been used for many years by many people without any unpleasant results reported. More recently, investigators in Canada have published a research paper outlining the safety of the micronutrients being studied. Data were assembled from all the known published and unpublished studies for the formula with the largest amount of published research in mental health. Biological safety data from 144 adults and children were available from six sources: there were no occurrences of clinically meaningful negative outcomes/effects or abnormal blood tests that could be attributed to toxicity (Simpson et al., 2011). In our trials conducted here at Canterbury, we have assessed hundreds of participants taking micronutrients for up to 4 months to date, and there were no abnormal results that concluded these micronutrients were having an adverse effect on liver or kidney function. Further, any side effects reported have been temporary and mild.

The most common ‘side effects’ are; relief from previously-experienced constipation and sleep improvement, i.e., positive side effects rather than adverse events. Other side effects that are reported by people taking micronutrients are headaches and stomach aches although they are typically mild and transitory. These difficulties can be avoided by taking capsules **on a full stomach**, so we suggest you *always take your capsules with food and plenty of water*. We will review side effects fortnightly and make a referral to a medical practitioner if necessary. We are happy to provide you with copies of the studies that have been done to date on EMPowerplus.

Micronutrients have the potential to interact with other medicines or drugs so you should avoid taking other medicines while taking the nutrients. For this reason, we are only including individuals in the study who *are not being concurrently treated for their illness using prescribed medications*. With respect to whether to take other medications, such as over the counter medications to treat colds, flu, stomach upset and sleep problems, because they may interact with the micronutrients, you

should first discuss with us or your pharmacist before use. **For safety reasons if you are, or become pregnant, you will have to withdraw from the study.**

Pregnancy should be avoided while taking the micronutrients. Further, we advise women that during the trial, if relevant, they use some form of contraception *because the safety of micronutrients during pregnancy has not been established (although there is no reason to think they are dangerous in such circumstances).*

### **Will I benefit if I take part?**

Everyone who takes part in this study will receive the micronutrients at some point during the trial. Previous research has shown that micronutrient formulas have a positive effect on insomnia, so you may benefit by taking part in this study. There is always a possibility that the micronutrients may not be effective for you; generally you must take the micronutrient formula for at least six weeks before an observable change occurs, therefore it is important that you keep on taking your assigned pills.

### **Do I have to participate?**

Absolutely not. Participation is voluntary and you have the right to withdraw from the project at any time without penalty. This decision will not influence your ongoing health care in any way. Similarly, the study's investigators may choose to end your participation in the study at any time for any reason. If new information becomes available that might affect your willingness to participate in the study, you will be informed as soon as possible. If you choose to withdraw, I will use my best endeavors to remove any of the information relating to you from the project, including any final publication, provided that this remains practically achievable.

### **Will I be paid for participating, or do I have to pay for anything?**

Arrangements will be made with each individual participant to ensure that your transportation costs to the university (to meet with the investigator) and parking are covered. The capsules you will be taking during the study will be provided at no cost. A koha of a grocery voucher will be given to participants upon completion of the study.

### **Will my records be kept private?**

The results of the project may be published, but you are assured of the complete confidentiality of data gathered in this investigation: your identity will not be made public without your prior consent and is only shared within the context of the Mental Health and Nutrition Research Team. **Complete anonymity of identity cannot be guaranteed as with regards to this study, the researchers' will know the identities of the participants as there will be face to face meetings both at recruitment, and during the study in order to check for compliance to treatment and to check for side effects.** We will take particular care to ensure the confidentiality of all data gathered for this study. We will also take care to ensure anonymity in publications of the findings. Data will be stored in password

protected computer files on the University of Canterbury (UC) system and paper records held in locked storage in the Psychology Department. All hard-copy questionnaire data will be stored in a locked private research office, in a locked cabinet file in site at University of Canterbury. Neville Blampied, Julia Rucklidge, and Kathleen Liberty will have access to the data obtained during the study. After seven years have passed, paper records will be destroyed. My thesis will be a public document and will be available through the UC Library but it will contain no information that identifies any participant.

**What happens after the study?**

If you feel you have benefited at the end of the trial, and want to continue taking the micronutrients, it is commercially available. If you choose to purchase EMP+, we will provide the necessary information on how to purchase it in New Zealand.

The results of this research will be reported in a thesis held digitally in the UC library, reported on at professional and scientific conferences, submitted for publication in peer reviewed scientific articles, and may be publicized in the media. You may request the reports from this study. Please indicate to the researcher on the consent form if you would like a copy of the summary of results of the project.

**Who can I contact during the study if I have a question?**

The project is being carried out as a requirement for the degree of Master of Science in Psychology by Alison Carley (details above), under the supervision of Neville Blampied ([Neville.blampied@canterbury.ac.nz](mailto:Neville.blampied@canterbury.ac.nz)), Julia Rucklidge ([Julia.rucklidge@canterbury.ac.nz](mailto:Julia.rucklidge@canterbury.ac.nz)), and Kathleen Liberty ([Kathleen.liberty@canterbury.ac.nz](mailto:Kathleen.liberty@canterbury.ac.nz)). We will be pleased to discuss any concerns you may have about participation in the project as well as any questions you may have throughout the study. This project has been reviewed and approved by the University of Canterbury Educational Research Human Ethics Committee, and participants should address any complaints to The Chair, Educational Research Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch ([human-ethics@canterbury.ac.nz](mailto:human-ethics@canterbury.ac.nz)).

**EMPowerPlus Advanced Supplement Facts**

Amount Per Serving (2 capsules)*		% Daily Value
Vitamin A (as retinyl palmitate)	768 IU	16
Vitamin C (as ascorbic acid)	80 mg	134
Vitamin D (as cholecalciferol)	192 IU	48
Vitamin E (as d-alpha tocopheryl succinate)	48 IU	160
Thiamin (as thiamin mononitrate)	2.4 mg	160
Riboflavin	1.8 mg	106
Niacin (as niacinamide)	12 mg	60
Vitamin B6 (as pyridoxine hydrochloride)	4.8 mg	240
Folic acid	342 mcg	48
Vitamin B12 (as methylcobalamin)	120 mcg	2000
Biotin	144 mcg	48
Pantothenic acid (as calcium pantothenate)	2.9 mg	29
Calcium (as chelate)	176 mg	18
Iron (as chelate)	1.9 mg	10
Phosphorus (as chelate)	112 mg	11
Iodine (from Pacific kelp)	27.2 mcg	18
Magnesium (as chelate)	80 mg	20
Zinc (as chelate)	6.4 mg	43
Selenium (as chelate)	26.5 mcg	38
Copper (as chelate)	1 mg	48
Manganese (as chelate)	1.3 mg	65
Chromium (as chelate)	84 mcg	70
Molybdenum (as chelate)	20 mcg	27
Potassium (as chelate)	32 mg	1

Propriety blend: Choline bitartrate, DL-phenylalanine, citrus Bioflavonoids, Inositol, L-Glutamine, L-Methionine, Grape seed extract, Ginkgo biloba leaf extract, ermanium sesquioxide, Boron (as chelate), Vanadium (as chelate), Nickel (as chelate).

Other ingredients: capsule shell (gelatin, titanium dioxide) microcrystalline cellulose, glycine, citric acid, magnesium stearate, silicon dioxide, mineral wax

\*Amount per serving on this list is for 2 capsules. Participants need to be aware that they are taking 4x this amount (8 capsules per day).

## Is stress affecting your sleep?

### Participating in my Masters study may help you!

#### Insomnia means Sleep Problems!

Many teachers suffer stress. One of the biggest sources of stress for teachers is child behaviour problems. Stress may cause sleep problems such as:

- Lying awake for a long time
- Waking frequently
- Waking up too early in the morning
- Feel tired during the day

**Dietary Supplements** have helped other stressed people sleep, and we think it may work for teachers, who may have a special type of stress. This is what my study is about!

#### How long does the study take?

- 30 minute appointment – wherever suits you!
- 5 short meetings during the study.
- The study will run through Term 4 of school starting 10<sup>th</sup> October.
- **You will finish before Christmas!**

#### What do you need to do during the study?

- Take the dietary supplements
- Tick a sleep checklist each morning (5 minutes).
- Online questionnaire 6 times (10 minutes).

#### What do you get out of participating?

- You will gain the opportunity to achieve good sleep and a reduction in stress.
- **DISCOUNT** on the supplement after the study
- Gift voucher at trial completion

#### Why am I inviting you?

- You work in a school impacted by the earthquake.
- Associate Professor Kathleen Liberty said that teachers of these schools may be experiencing sleeping difficulties.



#### Who is supervising this research?

- Professor Neville ~~Blampied~~ – who helps supervise many of the micronutrient research projects at the University of Canterbury.
- Professor Julia ~~Rucklidge~~ – who is a well known researcher in the area of mental health and nutrition.
- Associate Professor Kathleen Liberty – who leads the Juniors Settling in and Learning Study.

## Appendix C: Screening Questionnaire

### Insomnia Screening Survey

Q1 The following questions are being asked in order to assess your eligibility to take part in this study, and to gain some background information on the types of people who will take part in this study. This research is aimed at exploring the effect of a micronutrient supplement on insomnia. The choice of a micronutrient supplement is based on previous research which indicates that micronutrients can lower levels of stress, anxiety, and intrusive thoughts which are all thought to negatively impact sleep. You are now invited to answer a series of questions. The questions will take approximately 30 minutes to complete. The information gained from this survey will be kept confidential. Your specific contact details are being requested in order for us to contact you if you are eligible, they will not be used for any other purposes.

Q2 I understand that the information that I provide will be used for the purposes of assessing my eligibility to take part in this study and that all personal information gained about me will be kept strictly confidential. I agree to answer the following questions about myself.

- ☐ I AGREE with the above conditions (1)
- ☐ I DISAGREE with the above conditions (2)

If I DISAGREE with the above c... Is Selected, Then Skip To End of Block

Q3 Please complete the following contact details so that we can contact you about the study

- First name (8)
- Last name (9)
- Email address (10)
- Cell phone (15)
- Home phone (16)
- Home Address (17)

Q4 I am aged 18 years or older.

- ☐ Yes (1)
- ☐ No (2)

If No Is Selected, Then Skip To End of Block

Q5 Are you a registered teacher with at least 2 years experience working full time?

- ☐ Yes (1)
- ☐ No (2)

If No Is Selected, Then Skip To End of Block

Q6 Do you have access to a computer and home internet connection?

- ☐ Yes (1)
- ☐ No (2)

If No Is Selected, Then Skip To End of Block

Q7 Do you have Sleep Apnoea?

- ☐ Yes (1)
- ☐ No (2)

If Yes Is Selected, Then Skip To End of Block

Q8 Are you pregnant or breastfeeding or intend to have children in the near future?

☐ Yes (1)

☐ No (2)

If Yes Is Selected, Then Skip To End of Block

Q9 Do you currently have a child that is 2 years or under?

☐ Yes (1)

☐ No (2)

If Yes Is Selected, Then Skip To End of Block

Q10 Are you currently taking any psychoactive medications on a regular basis? These include antidepressants, anxiety medications, Ritalin, sleep medications etc.

☐ Yes (1)

☐ No (2)

Display This Question:

If Are you currently taking any psychoactive medication... Yes Is Selected

Q11 Please indicate which psychoactive or sleep medications you are currently taking, and how long you have been taking them

☐ 1. (1) \_\_\_\_\_

☐ 2. (2) \_\_\_\_\_

☐ 3. (3) \_\_\_\_\_

☐ 4. (4) \_\_\_\_\_

☐ 5 (5) \_\_\_\_\_

Q12 Are you currently taking any other types of medications?

☐ Yes (1)

☐ No (2)

Display This Question:

If Are you currently taking any medications? Yes Is Selected

Q13 Which medications are you currently taking?

Q14 Are you currently taking any herbal or nutritional supplements or formulas? (e.g vitamins, omega 3s, melatonin, St John's Wort)

☐ Yes (1)

☐ No (2)

Display This Question:

If Are you currently taking any other herbal or nutritional ... Yes Is Selected

Q15 Please indicate which nutritional supplements you are currently taking and how long you have been taking them.

1. (1)

2. (2)

3. (3)

4. (4)

5. (5)

Q16 Have you ever been described as having any of the following? Please indicate if this was in the past or currently.



	You suffered in the past		You are currently suffering	
	Yes (1)	No (2)	Yes (1)	No (2)
Anxiety disorder (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Major Depressive disorder (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dysthymia (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Bipolar disorder (mania depression) (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Psychotic disorder (schizophrenia) (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Behavioral problems (e.g., ADHD) (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Problems with drugs and/or alcohol (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Learning problems (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Neurological disorder (e.g., epilepsy, MS, narcolepsy) (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

If Neurological disorder (e.g.... Is Selected, Then Skip To End of Block

Q17 What is your date of birth?

Day (1)

Month (2)

Year (3)

Q18 What is your gender?

☐ Male (1)

☐ Female (2)

Q19 Please indicate which of the following ethnic groups you belong to (you may select more than one).

☐ NZ European/Pakeha (1)

☐ NZ Maori (2)

☐ Samoan (3)

☐ Tongan (4)

☐ Niuean (5)

☐ Chinese (6)

☐ Indian (7)

☐ Other (8) \_\_\_\_\_

Q20 Please indicate your highest educational qualification using the list below:

- ☐ University Bursary or Scholarship (4)
- ☐ Overseas qualification (5)
- ☐ Post-secondary (e.g., diploma, trade certificate) (6)
- ☐ University degree (7)
- ☐ Other qualification (8) \_\_\_\_\_

Q22 Please indicate which of the following best describes your total household income before tax (include income from all sources):

- ☐ less than \$20,000 (1)
- ☐ from \$20,000 to \$40,000 (2)
- ☐ from \$40,000 to \$60,000 (3)
- ☐ from \$60,000 to \$80,000 (4)
- ☐ more than \$80,000 (5)

Q23 Do you have a serious medical condition for which major medical interventions are happening over the next month?

- ☐ Yes (1)
- ☐ No (2)

Display This Question:

If Do you have a serious medical condition for which major m... Yes Is Selected

Q24 What is the serious medical condition?

Q25 Have you recently taken an oral antibiotic?

- ☐ No (1)
- ☐ Yes in the past 2 weeks (2)
- ☐ Yes in the past 4 weeks (3)
- ☐ Yes in the past 6 weeks (4)
- ☐ Yes, more than 6 weeks ago (5)

Q26 Are you currently taking an oral antibiotic?

- ☐ Yes (1)
- ☐ No (2)

Display This Question:

If Are you currently taking an oral antibiotic? Yes Is Selected

Q27 How long have you been taking the antibiotic?

Display This Question:

If Are you currently taking an oral antibiotic? Yes Is Selected

Q28 For what symptoms or health condition have you been taking the oral antibiotic?

Q29 Please indicate if you suffer from any kind of illness indicated below (you can select more than one option).

- ☐ Renal (1)
- ☐ Hepatic (2)
- ☐ Cardiovascular (3)
- ☐ Respiratory (4)
- ☐ None (5)

Display This Question:

- If Please indicate if you suffer from any kind of disease in... Renal Is Selected  
Or Please indicate if you suffer from any kind of disease in... Hepatic Is Selected  
Or Please indicate if you suffer from any kind of disease in... Cardiovascular Is Selected  
Or Please indicate if you suffer from any kind of disease in... Respiratory Is Selected

Q30 Please, specify which kind of disease you suffer from:

Q31 Do you have thyroid problems?

- ☐ Yes (1)  
☐ No (2)

Display This Question:

If Do you have thyroid problems Yes Is Selected

Q32 If you have thyroid problems choose the best answer from the drop down box that best describes your CURRENT thyroid functioning.

- ☐ Under control/stabilised (1)  
☐ Unstable (2)  
☐ Hyperthyroid (3)  
☐ Hypothyroid (4)

Q33 Do you have digestive problems or bowel-related problems (e.g., Chrohn's disease, ulcerative colitis, haemorrhoids, other)?

- ☐ Yes (1)  
☐ No (2)

Display This Question:

If Do you have digestive problems or bowel-related problems ... Yes Is Selected

Q34 Please, specify which kind of digestive or bowel-related problem you have.

- Click to write Choice 1 (1)  
Click to write Choice 2 (2)  
Click to write Choice 3 (3)  
Click to write Form field 4 (4)

Q35 Thank you for your participation. Unfortunately you are not eligible for this study. For any further information on counseling and sleep disorder services in Christchurch, please visit our website <http://bit.ly/UCnutritionresearch>

Q36 Instructions: Below is a list of common sleep complaints. During the past month, how many nights or days per week have you had the following symptoms?

	Never (1)	Do not know (2)	Rarely (less than once per week) (3)	Sometimes (1-2 times per week) (4)	Frequently (3-4 times per week) (5)	Always (5-7 times per week) (6)
1. Difficulty falling asleep. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q37 Has this symptom lasted for longer than 4 weeks?

- ☐ Yes (1)  
☐ No (2)

Q38 During the past month, how many nights or days per week have you had the following symptoms?

	Never (1)	Do not know (2)	Rarely (less than once per week) (3)	Sometimes (1-2 times per week) (4)	Frequently (3-4 times per week) (5)	Always (5-7 times per week) (6)
2. Difficulty staying asleep. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q39 Has this symptom lasted for longer than 4 weeks?

- ☐ Yes (1)  
☐ No (2)

Q40 During the past month, how many nights or days per week have you had the following symptoms?

	Never (1)	Do not know (2)	Rarely (less than once per week) (3)	Sometimes (1-2 times per week) (4)	Frequently (3-4 times per week) (5)	Always (5-7 times per week) (6)
3. Frequent awakenings from sleep. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q41 During the past month, how many nights or days per week have you had the following symptoms?

	Never (1)	Do not know (2)	Rarely (less than once per week) (3)	Sometimes (1-2 times per week) (4)	Frequently (3-4 times per week) (5)	Always (5-7 times per week) (6)
4. Feeling that your sleep is not sound. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q42 During the past month, how many nights or days per week have you had the following symptoms?

	Never (1)	Do not know (2)	Rarely (less than once per week) (3)	Sometimes (1-2 times per week) (4)	Frequently (3-4 times per week) (5)	Always (5-7 times per week) (6)
5. Feeling that your sleep is unrefreshing. (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q43 Has this symptom lasted for longer than 4 weeks?

- ☐ Yes (1)  
☐ No (2)

Q44 Instructions: If you have experienced any sleep symptoms during the past month please choose the appropriate level to let us know how your sleep is affecting your daily life.

	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
6. How much do your sleep problems bother you? (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Have your sleep difficulties affected your work? (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Have your sleep difficulties affected your social life? (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Have your sleep difficulties affected other important parts of your life? (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Have your sleep difficulties made you feel irritable? (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Have your sleep problems cause you to have trouble concentrating? (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Have your sleep difficulties made you feel fatigued? (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. How sleepy do you feel during the day? (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q46 The following questions ask about your sleep in the past 7 days and nights. Please choose the one best answer for each question.

Q47 In the past week, how much were you bothered by:

	Not at all bothered (1)	Slightly bothered (2)	Moderately bothered (3)	Severely bothered (4)
1. One or more awakenings after getting to sleep (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Not getting enough sleep (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Sleep that doesn't fully refresh you (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q48 In the past week, how much were you bothered by:

	Not at all bothered (1)	Slightly bothered (2)	Moderately Bothered (3)	Severely bothered (4)
4. Poor alertness during the daytime (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Difficulty keeping your thoughts focused (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Others noticing you appeared tired or fatigued (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q49 In the past week, how much were you bothered by:

	Not at all bothered (1)	Slightly bothered (2)	Moderately bothered (3)	Severely bothered (4)
7. Too many difficulties to overcome (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Bad mood(s) because you had poor sleep (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Lack of energy because of poor sleep (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q50 In the past week, how much were you bothered by:

	Not at all bothered (1)	Slightly bothered (2)	Moderately bothered (3)	Severely bothered (4)
10. Poor sleep that interferes with your relationships (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Being unable to sleep (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Being able to do only enough to get by (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q51 Please choose the best answer for each question about the past week:

13. From the time you tried to go to sleep, how long did it take to fall asleep on the most nights?

- ☐ Less than 1/2 an hour (1)
- ☐ Between 1/2 to 1 hour (2)
- ☐ Between 1 to 3 hours (3)
- ☐ More than 3 hours or I didn't sleep (4)

Q52 14. If you woke up during the night, how long did it take to fall back to sleep on most nights?

- ☐ Less than 1/2 an hour (1)
- ☐ Between 1/2 to 1 hour (2)
- ☐ Between 1 to 3 hours (3)
- ☐ More than 3 hours or I didn't sleep (4)

Q53 15. Not counting times when you were awake in bed, how many hours of actual sleep did you get during the worst night?

- ☐ More than 7 hours (1)
- ☐ Between 4 to 7 hours (2)
- ☐ Between 2 to 4 hours (3)
- ☐ Less than 2 hours or I didn't sleep (4)

Q54 16. On how many days did you have trouble coping because of poor sleep?

- ☐ None or 1 day (1)
- ☐ On 2 or 3 days (2)
- ☐ On 4 or 5 days (3)
- ☐ On 6 or all days (4)

Q55 Over the past week, how would you rate:

	Excellent (1)	Good (2)	Fair (3)	Poor (4)
17. Your sleep quality, compared to most people (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Your satisfaction with your sleep (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. The regularity of your sleep (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. The soundness of your sleep (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q56 21. Please feel free to tell us about any aspects of your sleep or wakefulness we may have missed:

Q57 Please read each statement and select one of the choices which indicates how much the statement applied to you over the PAST WEEK. There are no right or wrong answers. Do not spend too much time on any statement. Please answer all questions in one sitting. Once you have completed these last questions, we will be in contact with you.

Q58 I found it hard to wind down (over the past week)

- ☐ Did not apply to me at all (1)
- ☐ Applied to me to some degree, or some of the time (2)
- ☐ Applied to me to a considerable degree, or a good part of time (3)
- ☐ Applied to me very much, or most of the time (4)

Q59 I was aware of dryness of my mouth (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q60 I couldn't seem to experience any positive feeling at all (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q61 I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion) (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)



Q62 I found it difficult to work up the initiative to do things (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q63 I tended to over-react to situations (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q64 I experienced trembling (e.g., in the hands) (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q65 I felt that I was using a lot of nervous energy (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q66 I was worried about situations in which I might panic and make a fool of myself (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q67 I felt that I had nothing to look forward to (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q68 I found myself getting agitated (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q69 I found it difficult to relax (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q70 I felt down-hearted and blue (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q71 I was intolerant of anything that kept me from getting on with what I was doing (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q72 I felt I was close to panic (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q73 I was unable to become enthusiastic about anything (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q74 I felt I wasn't worth much as a person (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q75 I felt that I was rather touchy (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q76 I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat) (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q77 I felt scared without any good reason (over the past week)

- ☐ Did not apply to me at all (0)
- ☐ Applied to me to some degree, or some of the time (1)
- ☐ Applied to me to a considerable degree, or a good part of time (2)
- ☐ Applied to me very much, or most of the time (3)

Q78 I felt that life was meaningless (over the past week)

- ☐ Did not apply to me at all (1)
- ☐ Applied to me to some degree, or some of the time (2)
- ☐ Applied to me to a considerable degree, or a good part of time (3)
- ☐ Applied to me very much or most of the time (4)

Q79 If you are eligible to take part in this study, we will be inviting you to meet with the researcher and have the opportunity to share information about your participation in the study. Please indicate which times you would be available to attend this initial appointment. You can select more than one time option (the following question will ask you to indicate preferred days).

- ☐ Mornings 9-12 noon (1)
- ☐ Afternoons 12-3pm (2)
- ☐ Evenings 3-6 pm (3)

Q80 Please indicate your preferred days to meet with us.

- ☐ Monday (1)
- ☐ Tuesday (2)
- ☐ Wednesday (3)
- ☐ Thursday (4)
- ☐ Friday (5)

Q81 This study will last approximately 3 months. Are you willing to participate in the study for this amount of time?

- ☐ Yes (1)
- ☐ No (2)

Q82 Thank you very much for your time, your participation has been very important to us. We will contact you if you are eligible for this study. In the meantime, please visit our website <http://bit.ly/UCnutritionresearch> for information on counseling and sleep disorder services in the Christchurch area.

## Appendix D: Consent Form

**Telephone:** +64 0273754496

**Email:** alison.carley@pg.canterbury.ac.nz

**Date:** 10/05/16



### **Investigating the Effect of Micronutrients on Insomnia in Teachers: A Multiple-Baseline Design**

#### **Consent Form for Teachers Experiencing Insomnia**

**Principle Investigator:** Alison Carley

**Other Investigators:** Professors Neville Blampied, Julia Rucklidge, and Associate Professor Kathleen Liberty

I have read and I understand the information sheet for volunteers taking part in the study designed to assess the impact of a micronutrient formula on insomnia in teachers. I have had the opportunity to ask questions and discuss this study, and I am satisfied with the answers that have been given. I understand that my participation in this study is voluntary (my choice) and that I may withdraw from the study at any time without penalty and this will in no way affect my continuing health care. I also understand that I may withdraw any information already provided.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports of this study. I understand that the micronutrients will be stopped if they should appear harmful to me. I understand the compensation provisions for this study. I have had time to consider whether to take part. I know who to contact if I have any side effects to the study, or if anything occurs which I would consider a reason to withdraw from the study. I know who to contact if I have any questions about the study.

I wish to receive a copy of the results  
YES/NO

*Participants should be advised that a significant delay may occur between data collection and publication of the results.*

I consent to being contacted 3 months after completion of the study regardless of whether I chose to continue to take the micronutrient formula and at that point I can choose whether to complete questionnaires.  
YES/NO

I consent to my name being placed in a separate database so that I can be contacted in the future should there be other studies for me to participate in with the understanding that I can choose whether to participate in such studies or not.  
YES/NO

I consent to the use of my data for future related studies, which have been given ethical approval from a University of Canterbury Research Human Ethics Committee.

YES/NO

I hereby consent to participate.

Signed:  Date:

Printed name:

Signature of person who gained consent:

Address for results:

The person who may be contacted about the research is:

**Principle Investigator: Alison Carley** [alison.carley@pg.canterbury.ac.nz](mailto:alison.carley@pg.canterbury.ac.nz)

**Or: Professors Neville Blampied & Julia Rucklidge, or Associate Professor Kathleen Liberty**

*A signed copy of this consent form has been given to you to keep for your records and reference.*

## Appendix E: Side Effect Questionnaire

Q25 Please answer yes or no if you have experienced any of the following symptoms in the PAST TWO WEEKS.

	Yes (1)	No (2)
Dry mouth (1)	<input type="radio"/>	<input type="radio"/>
Urinary retention (2)	<input type="radio"/>	<input type="radio"/>
Blurred vision (3)	<input type="radio"/>	<input type="radio"/>
Constipation (4)	<input type="radio"/>	<input type="radio"/>
Sedation/lethargy (5)	<input type="radio"/>	<input type="radio"/>
Sleep disruption (6)	<input type="radio"/>	<input type="radio"/>
Nightmares (7)	<input type="radio"/>	<input type="radio"/>
Change in appetite (8)	<input type="radio"/>	<input type="radio"/>
Skin rash (9)	<input type="radio"/>	<input type="radio"/>
Weight gain (10)	<input type="radio"/>	<input type="radio"/>
Headache (11)	<input type="radio"/>	<input type="radio"/>
Nausea (12)	<input type="radio"/>	<input type="radio"/>
Gastrointestinal disturbance/diarrhoea (13)	<input type="radio"/>	<input type="radio"/>
Abdominal pain (14)	<input type="radio"/>	<input type="radio"/>
Inability to achieve an erection (15)	<input type="radio"/>	<input type="radio"/>
Inability to achieve an orgasm (16)	<input type="radio"/>	<input type="radio"/>
Loss of libido (17)	<input type="radio"/>	<input type="radio"/>
Agitation (18)	<input type="radio"/>	<input type="radio"/>
Anxiety (19)	<input type="radio"/>	<input type="radio"/>

Q26 Any other symptoms

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Q27 If you have experienced ANY of the symptoms what have you done to remedy them?